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⑤ **Aminediol protease inhibitors.**

⑦ Novel aminediol compounds, pharmaceutical compositions containing these compounds, and methods of using these compounds in inhibiting retroviral protease, particularly useful in the treatment and/or prevention of HIV infection (AIDS).

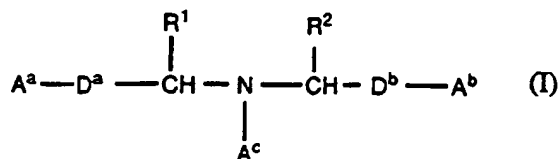
**EP 0 580 402 A2**

Field of the Invention

The present invention relates to novel aminediol compounds, to pharmaceutical compositions containing these compounds, and to methods of using these compounds in inhibiting the replication of retroviruses. The present invention particularly relates to novel aminediol compounds useful in the treatment and/or prevention of Acquired Immunodeficiency Syndrome (AIDS).

Summary of the Invention

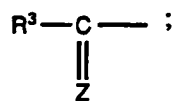
The present invention provides compounds of the following formula I:



where

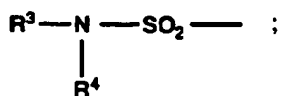
$A^a$ ,  $A^b$  and  $A^c$  are independently:

- (1) hydrogen;
- (2) alkyl, especially lower alkyl;
- (3)

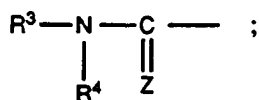


(4)  $R^3 - SO_2 -$  ;

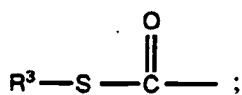
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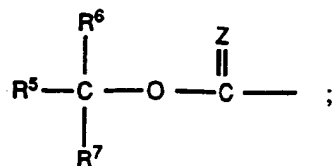


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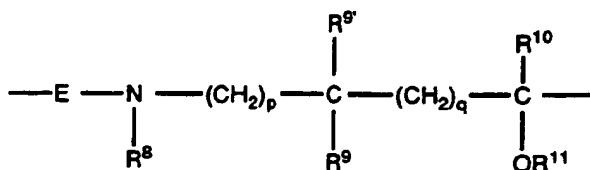


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or

(9)  $\text{R}^3\text{-SO-}$  ; $\text{D}^a$  and  $\text{D}^b$  are independently selected from groups of the formula:

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where  $\text{D}^a$  and  $\text{D}^b$  are bonded to the groups  $\text{A}^a$  and  $\text{A}^b$ , respectively, through the moiety  $-\text{E}-\text{N}(\text{R}^8)-$ , where E is a single bond or a peptide chain containing 1 to 4 amino acids, the N-terminus of which is bonded to  $\text{A}^a$  when E is part of  $\text{D}^a$  or to  $\text{A}^b$  when E is part of  $\text{D}^b$ ;

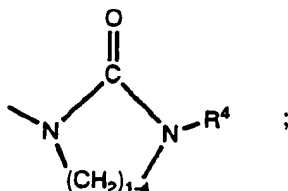
 $\text{R}^1$  and  $\text{R}^2$  are independently:

- (1) hydrogen;
- (2) alkyl, especially lower alkyl;
- (3) alkenyl, especially lower alkenyl;
- (4) aryl;
- (5) heterocyclo; or
- (6) carbocyclo, such as cycloalkyl;

 $\text{R}^3$  and  $\text{R}^4$  are independently:

- (a) hydrogen;
- (b) alkyl, especially lower alkyl;
- (c) aryl;
- (d) heterocyclo;
- (e) carbocyclo, such as cycloalkyl;
- (f) when  $\text{R}^3$  and  $\text{R}^4$  are bonded to a common nitrogen atom,  $\text{R}^3$  and  $\text{R}^4$  may be joined, together with that nitrogen atom, to form a heterocyclic ring system, such as a 5 to 7 membered heterocyclic ring; or
- (g) when E is a single bond and  $\text{R}^3$  is part of  $\text{A}^a$  or  $\text{A}^b$ ,  $\text{R}^3$  may, together with  $\text{R}^8$ , form an alkylene group, for example, having one to five carbons, such as wherein  $\text{R}^3$  and  $\text{R}^8$ , together with the atoms to which they are bonded, form the cyclic moiety:

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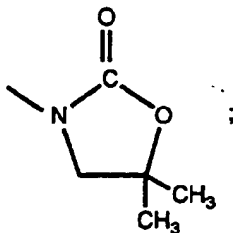


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 $\text{R}^5$ ,  $\text{R}^6$  and  $\text{R}^7$  are independently:

- (a) hydrogen;
- (b) alkyl, especially lower alkyl;
- (c) aryl;
- (d) carbocyclo, such as cycloalkyl;

- ( ) fluorenyl;  
 (f) heterocyclo;  
 (g)  $R^5$ ,  $R^6$  and  $R^7$  may, independently, be joined, together with the carbon atom to which they are bonded, to form a mono-, bi- or tricyclic carbocyclic ring system, especially wherein each ring contains 3 to 7 carbon atoms, or a mono-, bi- or tricyclic heterocyclic ring system;  
 (h) alkynyl;  
 (i) alkenyl; or  
 (j) when E is a single bond and  $R^5$ ,  $R^6$  and  $R^7$  are part of  $A^a$  or  $A^b$ , one of  $R^5$ ,  $R^6$ , or  $R^7$  may, together with  $R^8$ , form an alkylene group, for example, having one to three carbons, such as wherein  $R^5$  and  $R^6$  are methyl and  $R^7$  and  $R^8$ , together with the atoms to which they are bonded, form the cyclic moiety:



$R^8$  is:

- (a) hydrogen;  
 (b) alkyl, especially unsubstituted lower alkyl or aryl-lower alkyl;  
 (c)  $R^8$  and  $R^9$  may be joined, together with the atoms to which they are bonded, to form a heterocyclic ring system, for example, a 5 to 7 membered monocyclic heterocyclic ring;  
 (d)  $R^8$  may be joined together with  $R^5$ ,  $R^6$  or  $R^7$  as described above;  
 (e)  $R^8$  may be joined together with  $R^3$  as described above; or  
 (f)  $R^8$  and  $R^{11}$  may be joined, together with the atoms to which they are bonded, to form a heterocyclic ring system, such as where  $R^8$  and  $R^{11}$  together are an alkylene group;

$R^9$  and  $R^9$ , are independently:

- (a) hydrogen;  
 (b) alkyl, especially lower alkyl;  
 (c) alkenyl, especially lower alkenyl;  
 (d) alkynyl;  
 (e) aryl;  
 (f) heterocyclo;  
 (g) carbocyclo, such as cycloalkyl;  
 (h)  $R^9$  may be joined together with  $R^8$  as described above; or  
 (i)  $R^9$  and  $R^9$  may be joined, together with the carbon atom to which they are bonded, to form a carbocyclic group, such as 5- or 6-membered carbocyclic ring;

$R^{10}$  is:

- (a) hydrogen;  
 (b) alkyl, such as unsubstituted lower alkyl or hydroxy-lower alkyl, cycloalkyl-lower alkyl, aryl-lower alkyl or heterocyclo-lower alkyl;  
 (c) alkenyl, especially lower alkenyl;  
 (d) alkynyl;  
 (e) carbocyclo, such as cycloalkyl;  
 (f) aryl; or  
 (g)  $R^{10}$  and  $R^{11}$  taken together may form a bond to give a keto ( $C=O$ ) group;

$R^{11}$  is:

- (a) hydrogen;  
 (b) a hydroxyl protecting group, such as alkyl;  
 (c)  $R^{11}$  may be joined together with  $R^8$  as described above; or  
 (d)  $R^{11}$  may, together with  $R^{10}$ , form a bond to give a keto group as described above;

Z is oxygen or sulfur; and

p and q are, independently, integers from 0 to 4; and

salts, preferably pharmaceutically acceptable salts, thereof.



The compounds of the present invention inhibit the replication of retroviruses. The present invention thus also provides methods, and pharmaceutical compositions, for the treatment and/or prevention of diseases caused by such pathogenic organisms.

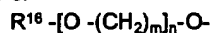
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#### Detailed Description of the Invention

The terms "alk" or "alkyl", as employed herein alone or as part of another group, denote both straight and branched chain, optionally substituted saturated radicals, for example, containing 1 to 12 carbons, most preferably 1 to 8 carbons, in the normal chain. It is understood, therefore, that throughout this specification the terms "alk" and "alkyl" denote both unsubstituted groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, n-hexyl and the like, as well as substituted groups such as phenylmethyl and the like. Exemplary substituents may include one or more, such as 1, 2 or 3, of the following:

- (1) hydroxy (or protected hydroxy);
- (2) oxo (i.e. = O), with the proviso that the carbon bearing the oxo group is not adjacent to a heteroatom;
- (3) carboxy;
- (4) halo (especially to form trihaloalkyl, particularly trifluoromethyl);
- (5) alkoxy, such as phenyl-lower alkoxy or

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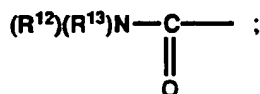


where m is an integer from 2 to 5; n is an integer from 1 to 5; and

R<sup>16</sup> is:

- (a) hydrogen;
- (b) alkyl, especially unsubstituted lower alkyl or alkoxy-lower alkyl;
- (c) aryl; or
- (d) heterocyclo;
- (6) aryloxy;
- (7) alkoxycarbonyl;
- (8)

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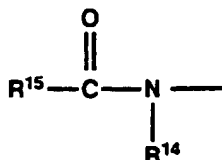
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where R<sup>12</sup> and R<sup>13</sup> are independently:

- (a) hydrogen;
- (b) alkyl, especially lower alkyl;
- (c) aryl;
- (d) heterocyclo;
- (e) carbocyclo, such as cycloalkyl;
- (f) R<sup>12</sup> and R<sup>13</sup> may be joined, together with the nitrogen atom to which they are bonded, to form a 5 to 7 membered heterocyclic ring;
- (9) (R<sup>12</sup>)(R<sup>13</sup>)N-, such as amino (H<sub>2</sub>N-);
- (10)

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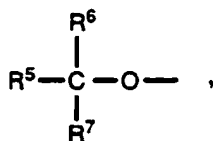
where R<sup>14</sup> is:

- (a) hydrogen;
- (b) alkyl, especially lower alkyl;
- (c) aryl;

- (d) heterocycle;  
 (e) carbocycle, such as cycloalkyl; or  
 (f) R<sup>14</sup> and R<sup>15</sup> may be joined to form an alkyl group of three to five carbon atoms; and

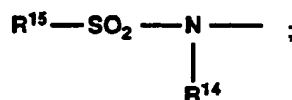
R<sup>15</sup> is:

- (a) hydrogen;  
 (b) alkyl, especially lower alkyl;  
 (c) alkenyl, especially lower alkenyl;  
 (d) aryl;  
 (e) heterocycle;  
 (f) carbocycle, such as cycloalkyl;  
 (g)



wherein R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are, independently, those groups (a) through (i) recited for R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> above;  
 or

- (h) R<sup>15</sup> may be joined together with R<sup>14</sup> as described above;  
 (11)



- (12) carbocycle, such as cycloalkyl;  
 (13) heterocycle;  
 (14) heterocycloxy;  
 (15) aryl;  
 (16) alkylcarbonyloxy, such as lower alkylcarbonyloxy;  
 (17) arylcarbonyloxy;  
 (18) cyano;  
 (19) mercapto;  
 (20) alkenyl;  
 (21) alkynyl, such as ethynyl (e.g., forming a propargyl group);  
 (22) alkylthio;  
 (23) arylthio;  
 (24) trialkylsilyl, such as trimethylsilyl;  
 (25) azo (i.e., R<sup>16</sup>O-N= where R<sup>16</sup> is as defined above, preferably hydrogen (to form an oxime group (HO-N=)) or unsubstituted alkyl (to form an unsubstituted alkoxyimino group (alkyl-O-N=)); or  
 (26) (R<sup>12</sup>)(R<sup>13</sup>)N-C(O)-O-, where R<sup>12</sup> and R<sup>13</sup> are as defined above.

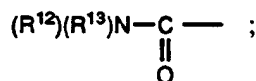
The term "alkoxy" denotes an alkyl group bonded through an oxygen bridge (-O-); the term "alkylthio" denotes an alkyl group bonded through a sulfur bridge (-S-); the term "alkoxycarbonyl" (also referred to as "carboalkoxy") denotes an alkoxy group attached to a carbonyl group to form an ester; the term "alkylcarbonyloxy" denotes an alkyl group bonded to a carbonyl group which is in turn bonded through an oxygen bridge; the term "aminocarbonyloxy" denotes an amino group bonded through a carbonyl group which is, in turn, bonded through an oxygen bridge; the term "alkylaminocarbonyloxy" denotes an alkyl group bonded through an aminocarbonyloxy group as described above; the term "alkylaminocarbonyl" denotes an alkyl group bonded through an amino group which is, in turn, bonded through a carbonyl group; and the term "alkylene" denotes a divalent alkyl group. With respect to exemplary alkyl groups which are substituted, the term "alkoxy-alkyl" specifically denotes an alkoxy group bonded through an alkyl group; the term "aryl-alkyl" specifically denotes an aryl group bonded through an alkyl group; the term "heterocyclo-alkyl" specifically denotes a heterocyclo group bonded through an alkyl group; the term "cycloalkyl-alkyl" specifically denotes a cycloalkyl group bonded

through an alkyl group; and the term "hydroxy-alkyl" specifically denotes one or more hydroxyl groups attached to an alkyl group. In each of the aforementioned terms, "alkyl" may be further substituted, or unsubstituted, as defined above. Likewise, "fluorenylalkyl" specifically denotes a fluorenyl group bonded through alkyl. Similarly, the terms "arylalkoxy", "alkoxyalkoxy", "hydroxyalkoxy", "heterocycloalkoxy", "aminoalkoxy", "aminocarbonylalkoxy", "heterocyclocarbonylalkoxy", "heterocyclooxyalkoxy", "alkoxycarbonylalkoxy" and "carboxyalkoxy" specifically denote alkoxy substituted by aryl, alkoxy, hydroxy, heterocyclo, amino, aminocarbonyloxy, heterocyclocarbonyl, heterocyclooxy, alkoxycarbonyl and carboxy, respectively.

The term "lower alkyl", as employed herein alone or as part of another group, denotes optionally substituted groups as described above for alkyl containing 1 to 6 carbon atoms in the normal chain. Lower alkyl groups are preferred alkyl groups.

The term "alkenyl", as employed herein alone or as part of another group, denotes both straight and branched chain, optionally substituted radicals, for example, containing 2 to 12 carbons in the normal chain, most preferably 2 to 8 carbons, which contain at least one carbon to carbon double bond and which are directly attached through one of the carbons composing the double bond. It is understood, therefore, that throughout this specification, the term "alkenyl" denotes both unsubstituted groups such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, and the like, as well as substituted groups. Exemplary substituents may include one or more, such as 1, 2 or 3, of the following:

- (1) alkyl, especially lower alkyl;
- (2) aryl;
- (3) carbocyclo, such as cycloalkyl;
- (4) heterocyclo;
- (5) carboxy;
- (6) halo;
- (7)

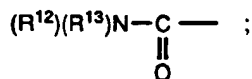


- (8) cyano;
- (9) alkoxycarbonyl;
- (10) trialkylsilyl; or
- (11) alkynyl.

The term "lower alkenyl", as employed herein alone or as part of another group, denotes optionally substituted groups as described above for alkenyl containing 2 to 6 carbon atoms in the normal chain. Lower alkenyl groups are preferred alkenyl groups.

The term "alkynyl", as employed herein alone or as part of another group, denotes both straight and branched chain, optionally substituted radicals, for example, containing 2 to 12 carbons in the normal chain, most preferably 2 to 8 carbons, which contain at least one carbon to carbon triple bond and which are directly attached through one of the carbons composing the triple bond. It is understood, therefore, that throughout this specification, the term "alkynyl" denotes both unsubstituted groups such as ethynyl, methyl-ethynyl, and the like, as well as substituted groups. Exemplary substituents may include one or more, such as 1, 2 or 3, of the following:

- (1) alkyl, especially lower alkyl;
- (2) aryl;
- (3) carbocyclo, such as cycloalkyl;
- (4) heterocyclo;
- (5) carboxy;
- (6)



- (7) cyano;
- (8) alkoxycarbonyl;

(9) alk nyl; or

(10) trialkylsilyl.

The terms "carbocyclo", "carbocyclic" or "carbocyclic ring system", as employed herein alone or as part of another group, denote an optionally substituted, saturated or partially unsaturated, homocyclic carbon ring system, such as a cycloalkenyl ring system, which is partially unsaturated, or most preferably, a cycloalkyl ring system, which is fully saturated, wherein the aforementioned cycloalkenyl and cycloalkyl ring systems are, according to the above definition, optionally substituted. Such cyclic groups preferably contain from 1 to 3 rings and from 3 to 12, most preferably from 3 to 7, carbons per homocyclic ring. It is understood, therefore, that throughout this specification the terms "carbocyclo", "carbocyclic" and "carbocyclic ring system" denote both unsubstituted groups exemplified by monocyclic groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; bicyclic groups such as octahydronaphthalenyl, decalin, norbornyl, spirocycloheptyl (e.g., spiro[2.4]heptyl), spirocyclooctyl (e.g., spiro[3.4]octyl), spirocyclononyl (e.g. spiro[4.4]nonyl), and the like; and tricyclic groups such as adamantyl, as well as substituted groups. Exemplary substituents may include one or more, such as 1, 2 or 3, of the following:

(1) alkyl, especially lower alkyl;

(2) hydroxy (or protected hydroxy);

(3) halo;

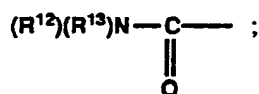
(4) mercapto;

(5) cyano;

(6) carboxy;

(7) alkoxy-carbonyl;

(8)



(9) alkylcarbonyloxy, such as lower alkylcarbonyloxy;

(10) arylcarbonyloxy;

(11) (R<sup>12</sup>)(R<sup>13</sup>)N-, such as amino (H<sub>2</sub>N-);

(12) alkoxy;

(13) aryl, such as where said aryl group is bonded through a single bond or is fused to said carbocyclo group (e.g. to form a tetrahydronaphthyl, indanyl or indenyl group), and wherein, in each case, the aryl-carbocyclo moiety so formed is bonded through the carbocyclo group;

(14) heterocyclo;

(15) heterocyclooxy;

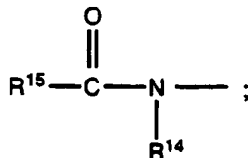
(16) oxo (= O);

(17) aryloxy;

(18) alkylthio;

(19) arylthio;

(20)



(21) alkenyl;

(22) alkynyl; or

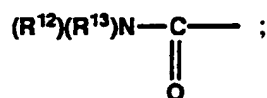
(23) trialkylsilyl.

The terms "ar" or "aryl", as employed herein alone or as part of another group, denote homocyclic, optionally substituted aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl and the like. It is understood,

therefor, that throughout this specification, the terms "ar" and "aryl" denote unsubstituted as well as substituted groups. Exemplary substituents may include one or more, such as 1, 2 or 3, of the following:

- (1) alkyl, especially lower alkyl;
- 5 (2) alkoxy;
- (3) hydroxy (or protected hydroxy);
- (4) halo;
- (5) (R<sup>12</sup>)(R<sup>13</sup>)N-, such as amino (H<sub>2</sub>N-);
- (6) alkylthio;
- 10 (7) mercapto;
- (8) nitro;
- (9) cyano;
- (10) carboxy;
- (11) carboalkoxy;
- 15 (12) carbocyclo, such as where said carbocyclo group is bonded through a single bond, or is fused to said aryl group (e.g. to form a tetrahydronaphthyl, indanyl or indenyl group), and wherein, in each case, the carbocyclo-aryl moiety so formed is bonded through the aryl group;
- (13)

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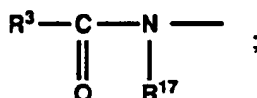


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(14) (R<sup>12</sup>)(R<sup>13</sup>)N-SO<sub>2</sub>-;

(15)

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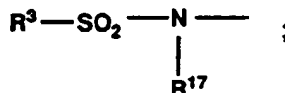


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where R<sup>17</sup> is:

- (a) hydrogen;
- (b) alkyl, especially lower alkyl;
- (c) aryl;
- (d) heterocyclo;
- 40 (e) carbocyclo, such as cycloalkyl; or
- (f) R<sup>17</sup> may, together with R<sup>3</sup>, form an alkylene group of three to five carbons;
- (16)

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- (17) phenyl;
- (18) alkylcarbonyloxy, such as lower alkylcarbonyloxy;
- (19) arylcarbonyloxy;
- (20) arylthio;
- (21) heterocycloxy;
- (22) aryloxy;
- 55 (23) alkylthio; or
- (24) alkyl.

The terms "arylcarbonyloxy" or "aryloxy" denote an aryl group which is bonded through a carbonyl group which is, in turn, bonded through an oxygen bridge; the term "arylthio" denotes an aryl group bonded through an oxygen bridge; the term "arylcarbonyl" denotes an aryl group bonded through a carbonyl group; the term

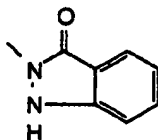
"arylamino" denotes an aryl group bonded through an amino group which is, in turn, bonded through a carbonyl group; and the term "arythio" denotes an aryl group bonded through a sulfur bridge.

The terms "halogen" or "halo", as employed herein alone or as part of another group, refer to chlorine, bromine, fluorine and iodine.

The terms "heterocyclo", "heterocyclic" or "heterocyclic ring system", as employed herein alone or as part of another group, denote an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclo group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclo group may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclo groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, 4-piperidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane, and tetrahydro-1,1-dioxothienyl, and the like.

Exemplary bicyclic heterocyclo groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolindinyl, quinolyl, tetra-hydroisoquinolyl, isoquinolyl, benzimidazolyl, benzopyranyl, indolizyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolyl, quinoxalyl, indazolyl, pyrrolopyridyl, dihydroindazolyl such as the group:

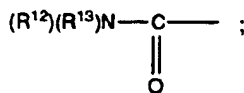


furo[2,3-c]pyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), and the like.

Exemplary tricyclic heterocyclo groups include carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl, and the like.

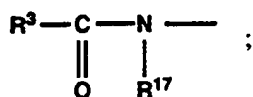
It is understood that throughout this specification the terms "heterocyclo", "heterocyclic" and "heterocyclic ring system" denote both unsubstituted as well as substituted groups. Exemplary heterocyclo substituents may include one or more, such as 1, 2 or 3, of the following:

- (1) alkyl, especially lower alkyl;
- (2) hydroxy (or protected hydroxy);
- (3) halo;
- (4) oxo (i.e. = O);
- (5)  $(R^{12})(R^{13})N-$ , such as amino ( $H_2N-$ );
- (6) alkoxy;
- (7) carbocyclo, such as cycloalkyl;
- (8) carboxy;
- (9) heterocycloxy;
- (10) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;
- (11)

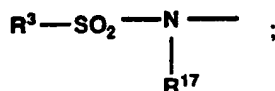


- (12) mercapto;
- (13) nitro;
- (14) cyano;

- (15) carboalkoxy;  
 (16)  $(R^{12})(R^{13})N-SO_2-$ ;  
 (17)



(18)



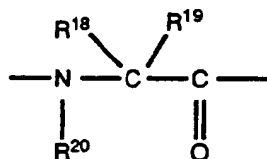
- (19) aryl;  
 (20) alkylcarbonyloxy;  
 (21) arylcarbonyloxy;  
 (22) arylthio;  
 (23) aryloxy;  
 (24) alkylthio; or  
 (25) formyl.

The term "heterocyclooxy" denotes a heterocyclo group bonded through an oxygen bridge; and the term "heterocyclocarbonyl" denotes a heterocyclo group bonded through a carbonyl group.

The term "hydroxyl protecting group", as used herein, denotes any group known as or capable of functioning as a hydroxyl protecting group, such as those groups so described in "Protective Groups in Organic Synthesis" by T.W. Greene, John Wiley and Sons, 1991, or Fieser & Fieser. Exemplary hydroxyl protecting groups include benzyl, trialkylsilyl, acetate and benzoate.

The term "carboxy", as used herein alone or as part of another group, denotes the carboxylic acid group -COOH.

The term "amino acid", as used herein alone or as part of another group, preferably denotes the group:



where  $R^{18}$  and  $R^{19}$  are independently:

- (1) hydrogen;  
 (2) alkyl, especially lower alkyl;  
 (3) alkenyl, especially lower alkenyl;  
 (4) aryl;  
 (5) heterocyclo;  
 (6) carbocyclo, such as cycloalkyl;  
 (7)  $R^{18}$  and  $R^{19}$  may be joined, together with the carbon atom to which they are bonded, to form a carbocyclo group, such as a 4- to 7-membered cycloalkyl ring; or  
 (8)  $R^{18}$  and  $R^{20}$  may be joined as described in the definition of  $R^{20}$  following;

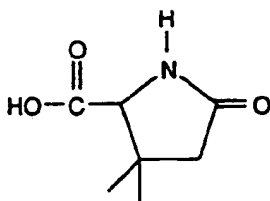
$R^{20}$  is:

- (1) hydrogen;  
 (2) alkyl, especially lower alkyl;  
 (3) aryl;  
 (4) heterocyclo;  
 (5) carbocyclo, such as cycloalkyl; or

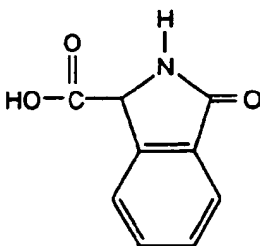
(6)  $R^{18}$  and  $R^{20}$  may be joined, together with the atoms to which they are bonded, to form a heterocyclic group, such as a 4 to 7 membered, saturated monocyclic heterocyclic ring which may be unsubstituted or substituted by groups such as:

- (i) hydrogen;
- (ii) alkyl, especially lower alkyl;
- (iii) alkenyl, especially lower alkenyl;
- (iv) aryl, for example, where said aryl group is bonded through a single bond, or is fused to said monocyclic heterocyclic ring to form an unsaturated bicyclic heterocyclic ring system;
- (v) heterocyclo;
- (vi) mercapto;
- (vii) alkoxy;
- (viii) carbocyclo, such as cycloalkyl, for example, where said cycloalkyl group is bonded through a single bond, or is fused or spirofused to said monocyclic heterocyclic ring to form a saturated bicyclic heterocyclic ring system;
- (ix) hydroxyl (or protected hydroxyl);
- (x) aryloxy;
- (xi) alkylthio;
- (xii) arylthio; or
- (xiii) oxo.

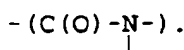
The amino acid moiety described above includes, for example, such moieties as may be found in D and L alanine, asparagine, aspartic acid, arginine, cysteine, glycine, glutamine, glutamic acid, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, homoserine, threonine, tryptophan, tyrosine, valine, hydroxyvaline, norleucine, norvaline, phenylglycine, cyclohexylalanine, t-butylglycine (t-leucine), hydroxy-t-butylglycine, amino butyric acid, ornithine, and cycloleucine, and preferably, when  $R^{18}$  and  $R^{20}$  are joined, together with the atoms to which they are bonded, proline, 4-hydroxyproline, pyroglutamic acid, azetidine carboxylic acid, pipercolinic acid, indoline-2-carboxylic acid, tetrahydro-3-isoquinoline carboxylic acid,



and



The term "peptide chain", as used herein, denotes two or more amino acids as described above bonded through a peptide linkage



The "N-terminus" of the above-described amino acid(s) denotes the  $-N(R^{20})-$  group.

The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases.

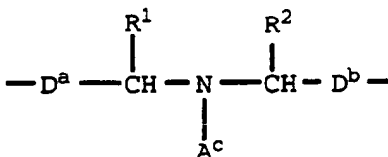


Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein, as are quaternary ammonium salts such as alkylammonium salts. The nontoxic, pharmaceutically acceptable salts are preferred, although other salts may be useful, for example, in isolation or purification steps which may be employed during preparation.

Exemplary acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

The present invention contemplates all compounds containing the moiety:



particularly such compounds capable of inhibiting retroviral, preferably HIV, protease.

Prodrugs and solvates of the inventive compounds are also contemplated herein. The term "prodrug", as employed herein, denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. See H. Bundgaard, "Drugs of the Future", 16 (5), 443-458 (1991); and H. Bundgaard (Ed), "Design of Prodrugs" 1985 Elsevier (Amsterdam), both incorporated herein by reference.

Solvates of the compounds of formula I are preferably hydrates. Tautomers of the inventive compounds are also contemplated, such as hemiketals of hydroxyketones, the enol form of ketones, and the like.

The initial definition provided for a group or term herein applies to that group or term throughout the present specification, unless otherwise indicated. It is to be understood that "exemplary" groups recited herein are illustrative and not limiting. It is particularly advantageous to employ those groups preceded by the terms "especially" or "preferably". Throughout this specification, groups and substituents thereof may be chosen to provide stable moieties and compounds.

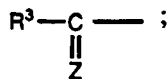
All stereoisomers of the present compounds are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

A description of exemplary methods for obtaining the compounds of the present invention follows. The reaction conditions of these methods, such as temperature, amount of reagent, pressure, reaction time, atmosphere and solvent employed may readily be ascertained by one of ordinary skill in the art.

In the following Reaction Schemes:

Q<sup>1</sup> and Q<sup>2</sup> are independently:

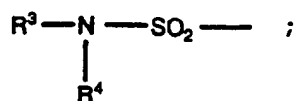
(1)



(2)  $R^3-SO_2^-$  ;

(3)

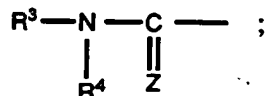
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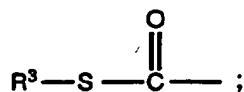
(4)

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(5)

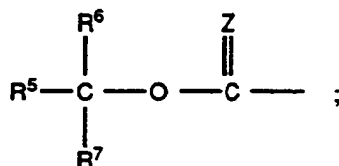
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(6)

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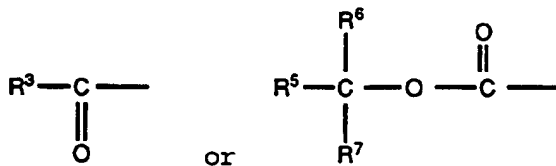
or

(7)  $R^3-SO-$  .

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The above Q<sup>1</sup> and Q<sup>2</sup> groups are preferably employed where indicated as they render the nitrogen atoms to which they are bonded non-basic. Where compounds of the invention are desired in which A<sup>a</sup> and/or A<sup>b</sup> are one of the above groups (1) to (7), the Q<sup>1</sup> or Q<sup>2</sup> groups of the following Reaction Schemes need not be removed. Where compounds of the invention are desired in which A<sup>a</sup> and/or A<sup>b</sup> are other than the above groups (1) to (7), Q<sup>1</sup> or Q<sup>2</sup>, for example, can be:

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(especially t-butoxycarbonyl (Boc) or carbobenzyloxy (Cbz)), forming amide and carbamate groups, respectively. These latter groups can be removed, and replaced with the desired A<sup>a</sup> and/or A<sup>b</sup> groups, by methods known in the art. With the exception of the conditions used for their optional removal, Q<sup>1</sup> and Q<sup>2</sup> groups are chosen that are stable to the conditions used in the following Reaction Schemes.

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Q<sup>3</sup> is:

(1) hydrogen; or

(2) alkyl.

The above Q<sup>3</sup> groups are preferably employed where indicated as they render the nitrogen atom to which they are bonded basic. Exemplary Q<sup>3</sup> groups are hydrogen, unsubstituted lower alkyl, alk-nyl-lower alkyl, and aryl-lower alkyl. Where compounds of the invention are desired in which A<sup>c</sup> is one of the above groups (1) or (2), the Q<sup>3</sup> group employed in the following Reaction Schemes need not be removed. Where compounds of the invention are desired in which A<sup>c</sup> is other than the above groups (1) or (2), Q<sup>3</sup> can, for example, be a benzyl group. The benzyl group may be removed and replaced by the desired A<sup>c</sup> group by methods known in the art. With the exception of the conditions used for their removal, Q<sup>3</sup> groups are chosen that are stable to the conditions used in the following Reaction Schemes.

In the following Reaction Schemes, where it is desired to remove Q<sup>1</sup>, Q<sup>2</sup> and/or Q<sup>3</sup> groups and to couple the amine groups so formed with another of the groups of A<sup>a</sup>, A<sup>b</sup> and/or A<sup>c</sup>, methods known to those of ordinary skill in the art may be employed (as exemplified by Methods (D), (E) and (F) of Reaction Scheme 11). For examples of amine protecting groups and their removal see Greene, "Protective Groups in Organic Synthesis," John Wiley (1991).

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Reaction Scheme 1  
Preparation of Intermediate Materials

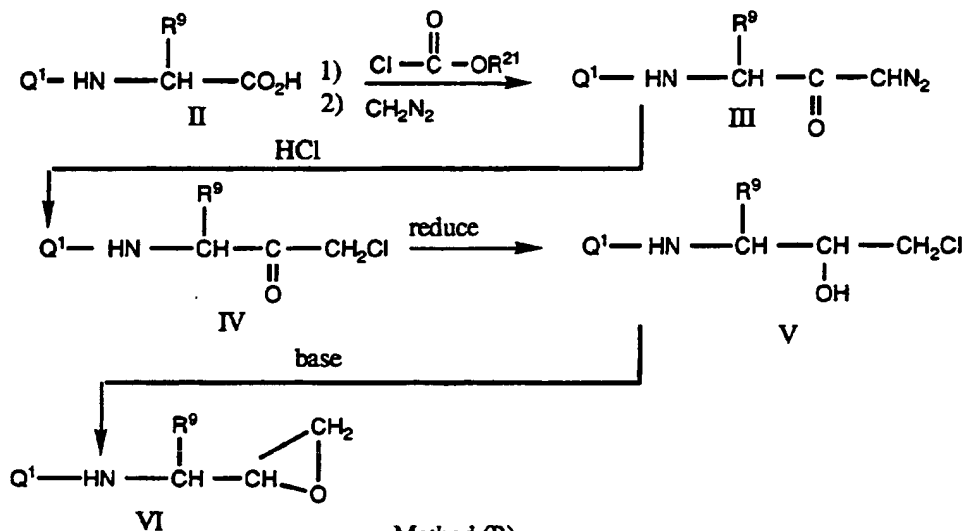
Method (A)

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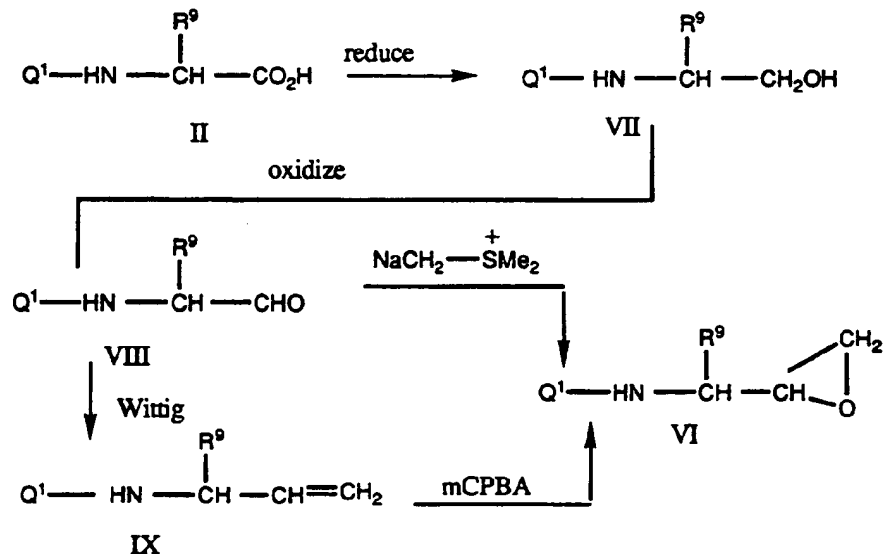
Method (B)

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55 Intermediate materials for the preparation of compounds of the formula I may be prepared by Methods (A) or (B) as shown in Reaction Scheme 1 above. Starting compounds II may readily be prepared by one of ordinary skill in the art by known methods, such as those described in Greene.

In Method (A), an N-protected amino acid II is converted to a reactive intermediate (not shown), such as to an acid chloride by reaction with thionyl chloride or oxalyl chloride, or to a mixed anhydride by reaction with a chloroformate of the formula Cl-C(O)-OR<sup>21</sup> where R<sup>21</sup> is an unsubstituted lower alkyl group, and then treated

with diazomethane to give the  $\alpha$ -chloroketone III. Treatment of III with HCl gives the  $\alpha$ -chloroketone IV, which may be converted to the chlorohydrin V by reduction, and then to the epoxide VI by reaction with a base by methods known in the art (see Handa et al., Eur. Pat. Appl. 346,847; Rich et al., J. Med. Chem., 34, 1222 (1991)).

5 For example, the  $\alpha$ -chloroketone IV may be reduced with a hydride reducing agent such as lithium aluminum hydride, sodium borohydride, lithium and/or potassium-selectride, potassium borohydride, diisobutylaluminum hydride, and the like to give the chlorohydrin V, which can be converted to the epoxide VI by treatment with a base such as sodium or potassium hydroxide, sodium or potassium hydride, or an alkylamine base such as triethylamine. Compound III may, alternatively, be treated with HBr to give the  $\alpha$ -bromoketone corresponding to  $\alpha$ -chloroketone IV. The corresponding  $\alpha$ -bromoketone may be prepared or employed wherever the  $\alpha$ -chloroketone IV is prepared or employed in the present Reaction Schemes (for example, to prepare the bromohydrin corresponding to chlorohydrin V).

An alternate procedure, Method (B), based upon methods known in the art (see Desolms et al., European Patent 356,223) may also be employed. This method involves reduction of the protected amino acid II to the alcohol VII using a reagent such as lithium aluminum hydride or borane (Brown et al., J. Amer. Chem. Soc., 82, 3866 (1960)) or via reduction of a mixed anhydride intermediate (formed as described above) with a hydride reducing agent such as sodium borohydride (Corey et al., J. Amer. Chem. Soc., 98, 6417 (1976)). The alcohol VII can be oxidized to the aldehyde VIII with a chromium (VI) reagent (Evans et al., J. Org. Chem., 47, 3016 (1982)), or via a Moffatt (Albright et al., J. Org. Chem., 30, 1107 (1965)) or Swern (Swern et al., J. Org. Chem., 43, 2480 (1978)) procedure. The aldehyde VIII may be converted directly to the epoxide VI via reaction with a sulfonium or arsonium ylide (Corey et al., J. Amer. Chem. Soc., 87, 1353 (1965); Still et al., J. Amer. Chem. Soc., 103, 1283 (1981)), or indirectly by a Wittig or Peterson (Peterson, J. Org. Chem., 33, 780 (1968)) reaction to give the olefin IX, followed by epoxidation with a reagent such as meta-chloroperoxybenzoic acid (mCPBA), peracetic acid, or the like.

25 In Method (B), the aldehyde VIII may also be produced from a carboxylic acid ester of the acid II (not shown) by reduction with diisobutylaluminum hydride (Ito et al., Chem. Pharm. Bull., 23, 3081 (1975)), or via reduction of the methyl hydroxamate with lithium aluminum hydride (Castro et al., Synthesis, 676 (1983)), and the aldehyde VIII converted to the epoxide VI as described above.

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## Reaction Scheme 2

Preparation of Compounds I where  $A^a = A^b$  and  $D^a = D^b$ 

## Method (A)

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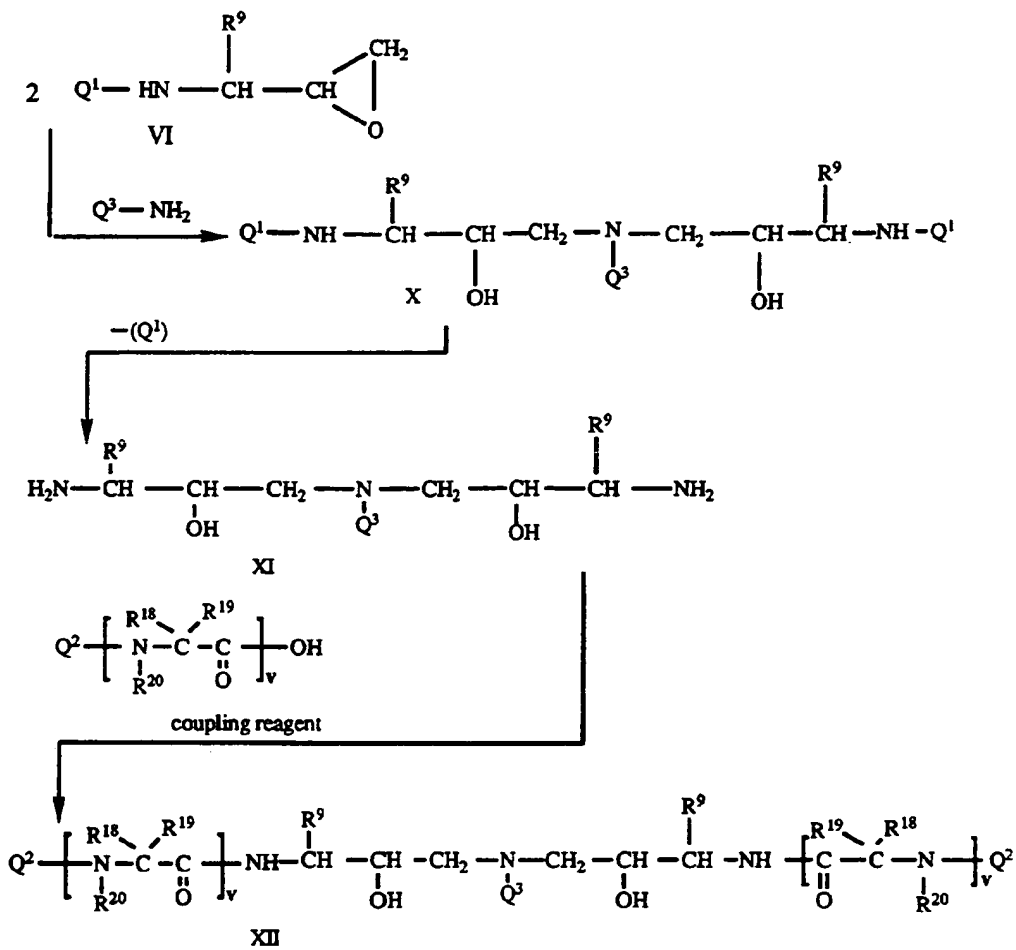
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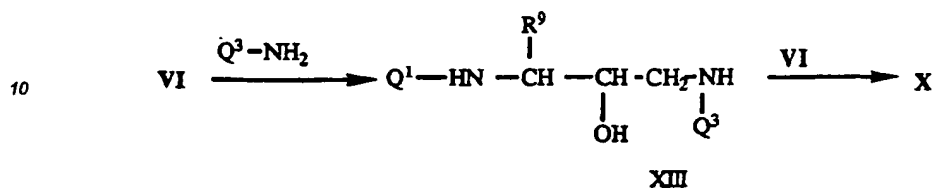
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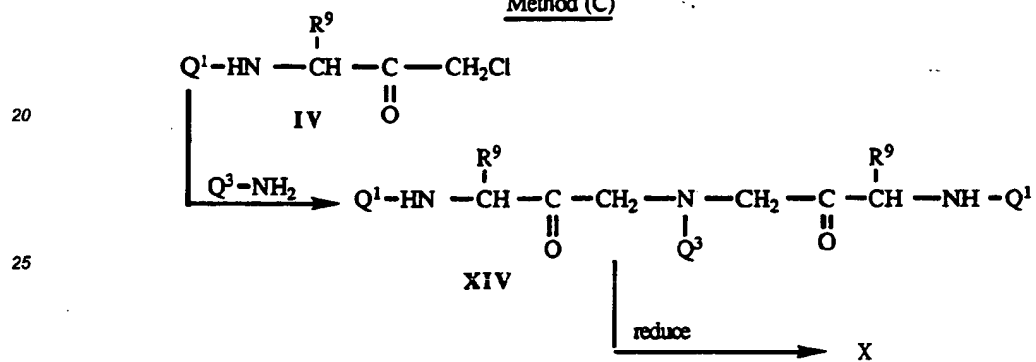


Reaction Scheme 2 (Cont'd)

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Method (B)

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Method (C)

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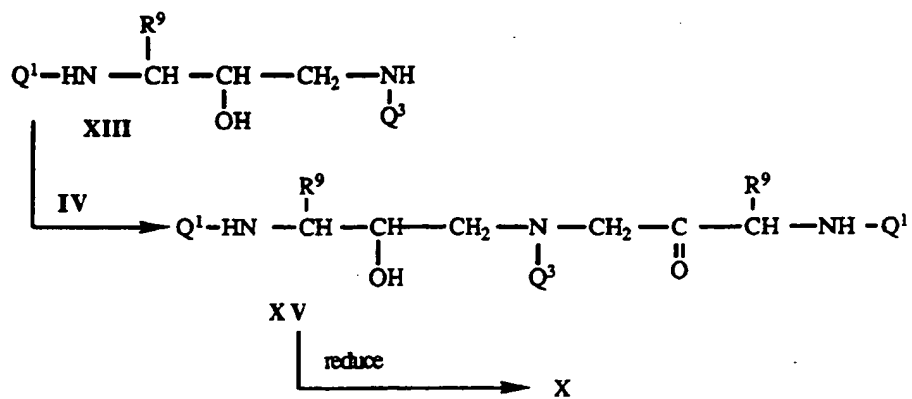
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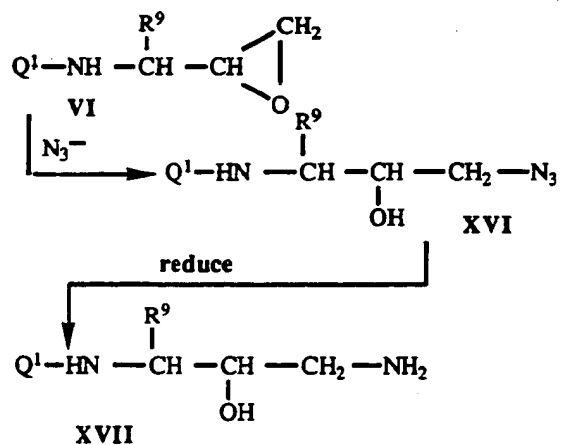
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## Reaction Scheme 2 (Cont'd)

## Method (D)

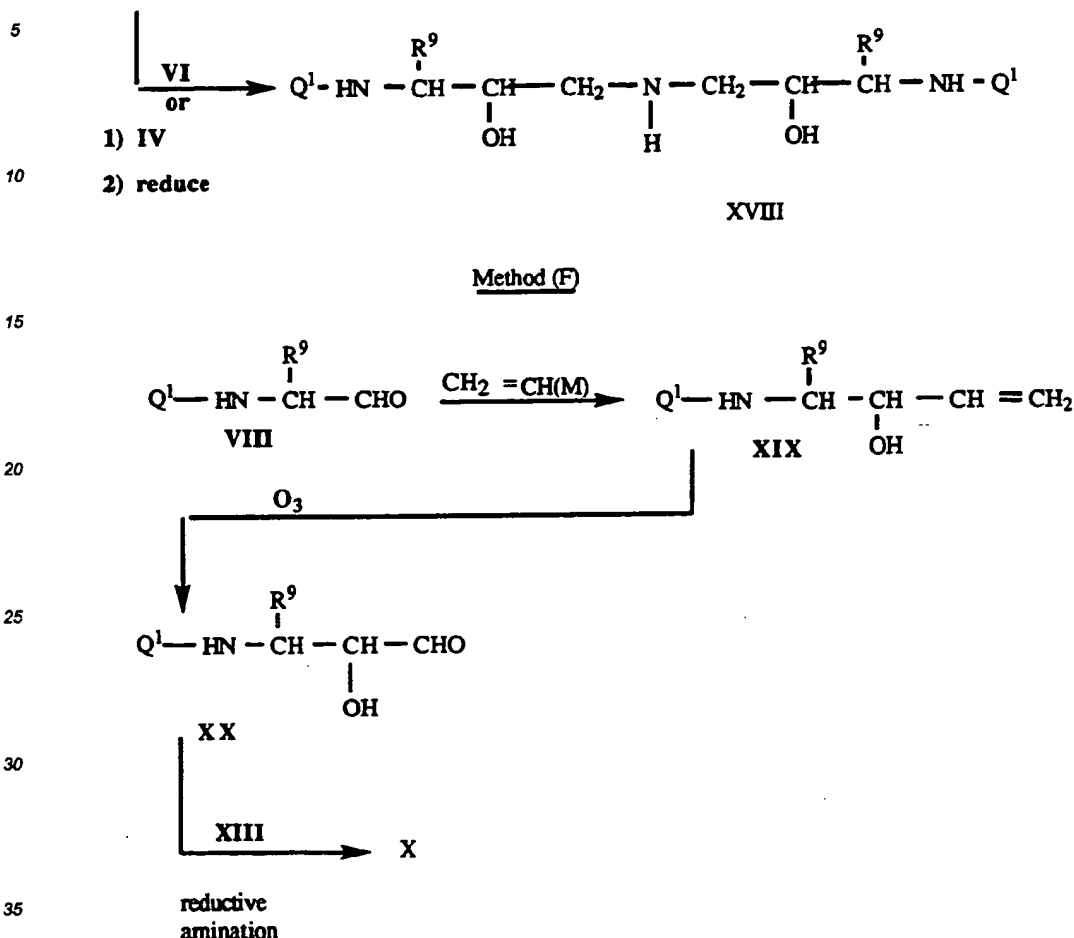


## Method (E)





## Reaction Scheme 2 (Cont'd)



Reaction Scheme 2 above illustrates Methods (A) through (F), which may be used to prepare compounds of the formula I where A<sup>a</sup> is the same as A<sup>b</sup> and D<sup>a</sup> is the same as D<sup>b</sup> ("symmetrical" compounds).

Method (A) begins by treating two equivalents of the epoxide VI with one equivalent of Q<sup>3</sup>-NH<sub>2</sub>, where Q<sup>3</sup> is preferably hydrogen, unsubstituted lower alkyl, alkenyl-lower alkyl (e.g. allyl) or aryl-lower alkyl (e.g. benzyl), particularly benzyl as described above, and heating in a solvent such as methanol or dimethylformamide (Parker et al., Chem. Rev., 59, 737 (1959); for alternative conditions, see Posner et al., J. Amer. Chem. Soc., 99, 8208 (1977); Overman, J. Org. Chem., 50, 4154 (1985); Tetrahedron Lett., 27, 2451 (1986)), giving the aminediol X.

The terminal groups Q<sup>1</sup> of the aminediol X may optionally be removed by methods known to the skilled artisan (Greene), and the resulting bis-amine XI coupled to an N-protected amino acid or peptide chain (prepared using standard solid or solution phase techniques as described in Bodanszky and Bodanszky, The Practice of Peptide Chemistry; pp. 89 - 150, Springer-Verlag, 1984, where Q<sup>2</sup> is described above and is compatible with the conditions used in the coupling reaction), using a coupling reagent such as dicyclohexylcarbodiimide (DCC), 3-ethyl-3'-(dimethylamino)propylcarbodiimide (EDCI), bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent), diphenylphosphoryl azide (DPPA) and the like, to give the aminediol XII. (For other methods see Bodanszky, Principles of Peptide Synthesis, pp. 9 - 58, Springer-Verlag (1984)). In the N-protected amino acid or peptide chain, v is an integer from 1 to 4. Where, in the bis-amine XI, Q<sup>3</sup> is hydrogen, the central nitrogen atom to which it is bonded ("central amine") may optionally be protected, and in the following Reaction Schemes where appropriate, the central amine may be protected by nitrogen protecting groups known in the art, for example, by an aryl-alkyl group such as benzyl or trityl, an alkyl-alkyl group such as allyl, as well as groups forming, to-

g th r with the c ntral nitrog n atom, a carbamate or amide group.

Methods (B) through (F), described following, illustrate alternate routes for obtaining compound X, which may optionally be further treated as described above in Method (A).

5 In Method (B), the proc ss may be carri d out in a step-wis fashi n by treatment of on quival nt f the epoxide VI with one equivalent or an excess of the primary amine or ammonia ( $Q^3-NH_2$ ) t give the amino alcohol XIII, which in turn may be coupled again to the epoxide VI to give X.

10 In Method (C), the process may be carried out by reaction of two equivalents of the chloroketone IV (or the corresponding bromoketone) with one equivalent of the aforementioned primary amine or ammonia ( $Q^3-NH_2$ , where  $Q^3$  is preferably benzyl), to form the diketoamine XIV, which may be reduced to the aminediol X with a hydride reducing agent such as lithium aluminum hydride, sodium or potassium borohydride, lithium or potassium selectride (i.e., lithium or potassium tri-sec-butylborohydride), diisobutylaluminum hydride, and the like.

15 In Method (D), a step-wise procedure can be carried out by coupling the aforementioned amino alcohol XIII with the chloroketone IV (or the corresponding bromoketone) (Gordon et al., J. Org. Chem., 51, 3073 (1986)) to give the ketohydroxyamine XV, which may be reduced by methods described above.

20 In Method (E), the epoxide VI may be opened with azide anion, such as by treatment with sodium azide, to give the azidoalcohol XVI (Ingham et al., J. Org. Chem., 21, 373 (1956); Rosenberg et al., J. Med. Chem., 32, 1371 (1989); Saito et al., Tetrahedron Lett., 30, 4153 (1989)). The azido moiety may be reduced to the amine by, for example, hydrogenation over Pd/C or by treatment with triphenylphosphine (Vaultier et al., Tetrahedron Lett., 24, 763 (1983)). The resulting aminoalcohol XVII can be coupled to the epoxide VI, or to the chloroketone IV (or the corresponding bromoketone) followed by reduction, as described above to give the aminodiol XVIII. The central amine may optionally be protected as described above, and the  $Q^1$  groups optionally removed and the resulting amines coupled to amino acids or peptide chains, also as described above.

25 In Method (F), the aminoaldehyde VIII can be reacted with a vinyl organometallic reagent of the formula  $CH_2=CH(M)$ , where M is a metal-containing moiety, such as vinyl lithium, vinyl magnesium bromide and the like to give the allylic alcohol XIX. The olefin moiety may be oxidatively cleaved to the aldehyde by ozonolysis, or the compound XIX converted to the corresponding diol (not shown) with osmium tetroxide or potassium permanganate, followed by cleavage of the diol with sodium periodate (Lemieux et al., J. Org. Chem., 21, 478 (1956)) to form the aldehyde. The aldehyde XX can then be reacted with the aminoalcohol XIII under reductive amination conditions (for example, hydrogenation over Pd/C or reaction with sodium cyanoborohydride where  $Q^3$  is hydrogen or benzyl; see Hudlicky, Reductions in Organic Chemistry, pp. 134 - 136, John Wiley, 1984) to give compound X.

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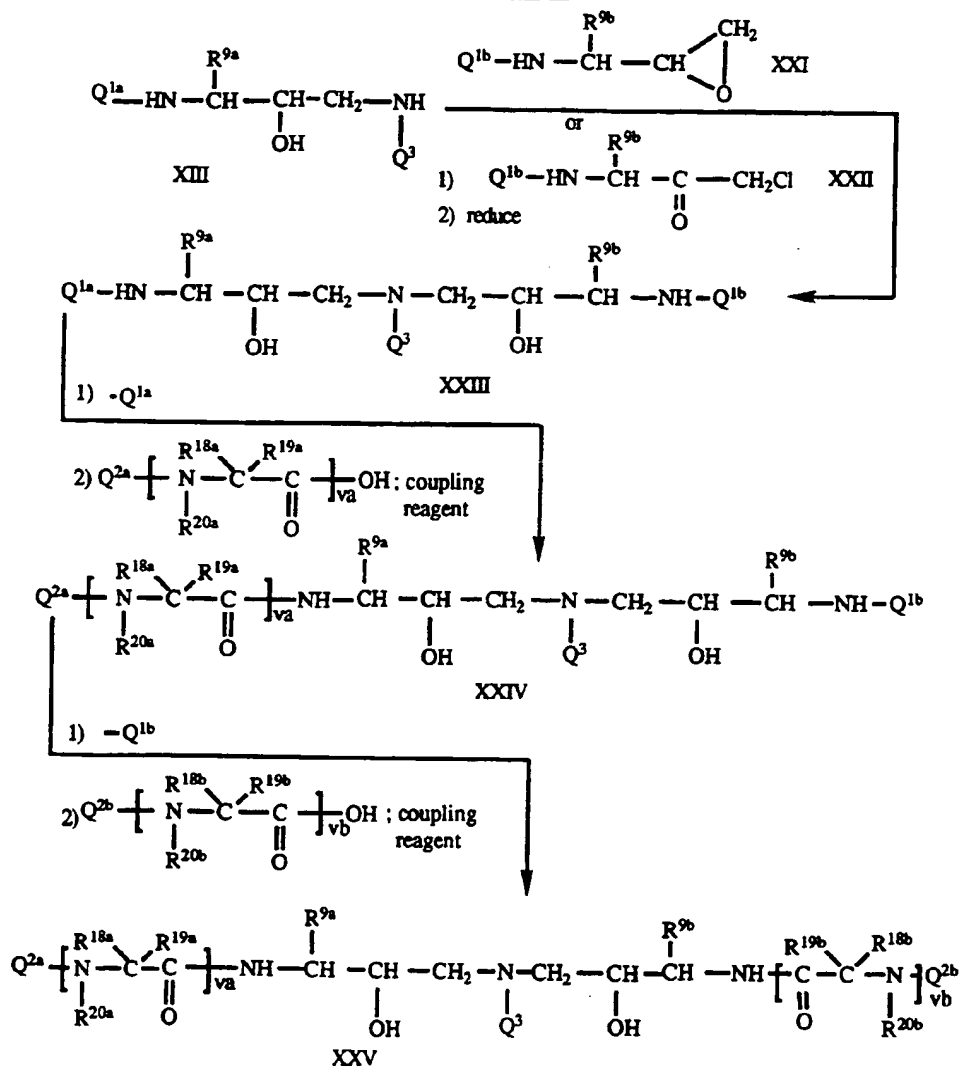
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## Reaction Scheme 3

Preparation of Compounds I where  $A^a \neq A^b$   
and/or  $D^a \neq D^b$

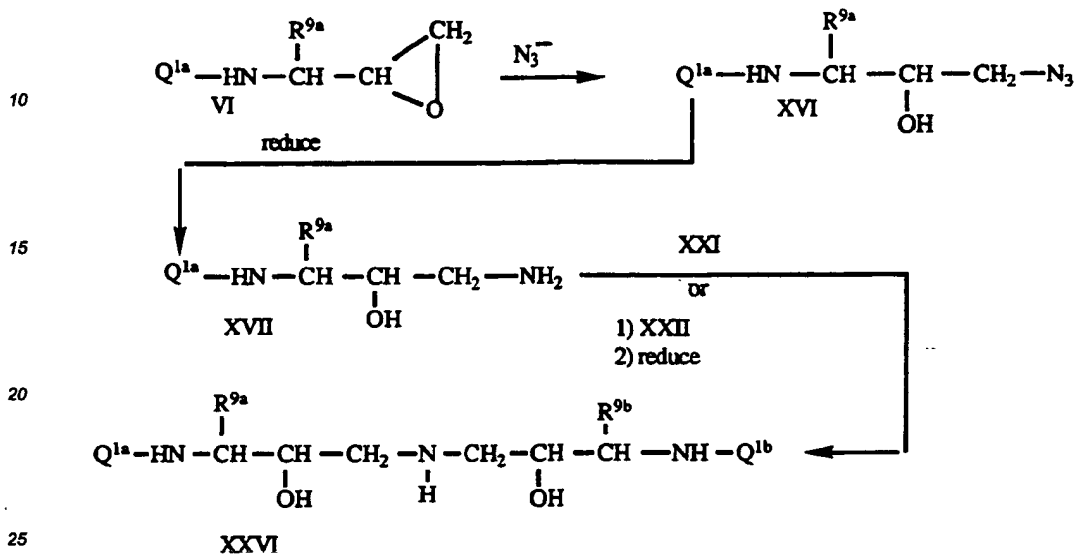
## Method (A)



## Reaction Scheme 3 (Cont'd)

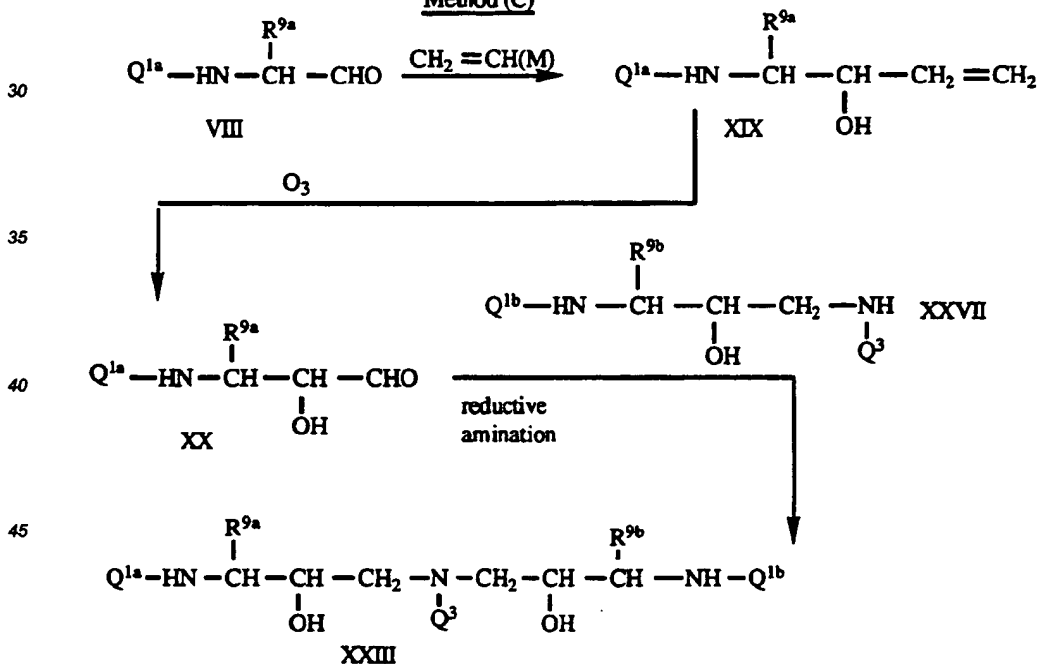
5

## Method (B)



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## Method (C)



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Reaction Scheme 3 above illustrates Methods (A) through (C), which may be used to prepare compounds of the formula I where A<sup>a</sup> differs from A<sup>b</sup> and/or D<sup>a</sup> differs from D<sup>b</sup> ("asymmetrical" compounds) by procedures analogous to those of Reaction Scheme 2. In Reaction Scheme 3, and hereinafter, the symbols "a" or "b" added to a moiety (e.g., R<sup>9a</sup>) denote those groups ultimately forming a part of the moiety A<sup>a</sup>-D<sup>a</sup>- or A<sup>b</sup>-D<sup>b</sup>-, respectively, in the compounds of formula I, or, in the case of Q<sup>1a</sup> or Q<sup>2a</sup> and Q<sup>1b</sup> or Q<sup>2b</sup>, denote those groups on the corresponding side of the molecule. Moieties to which the symbols "a" or "b" are added are otherwise defined as above (e.g., R<sup>9a</sup> is defined as for R<sup>9</sup>), although said moieties may be defined independently of each other (e.g., R<sup>9a</sup> may be defined independently of R<sup>9b</sup>).

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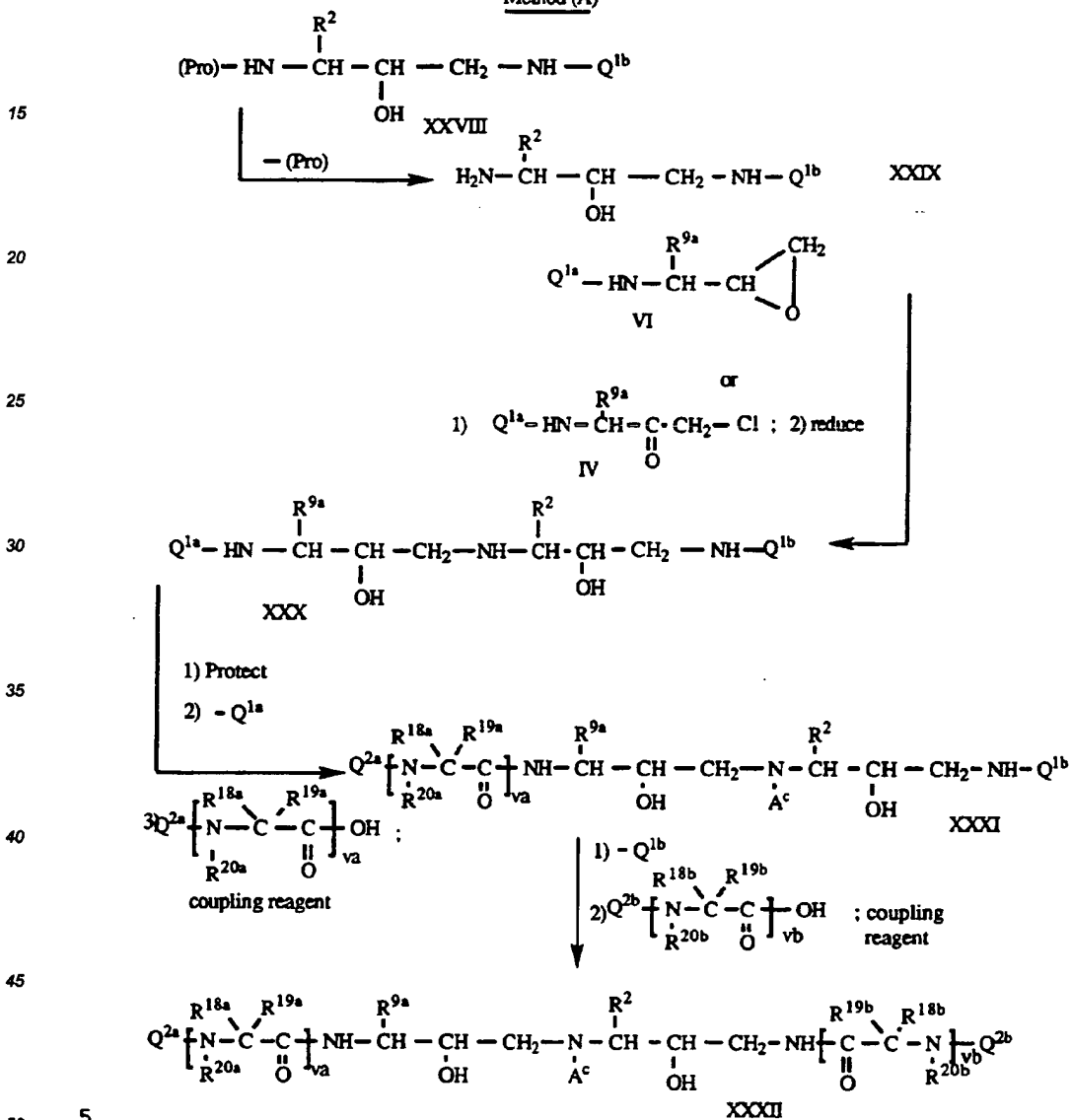
Method (A) of Reaction Scheme 3 begins by coupling the aminoalcohol XIII to the epoxide XXI (see Method (A) of Reaction Scheme 1 for preparation of epoxide XXI), or to the chloroketone XXII (see Method (A) of Reaction Scheme 1 for preparation of chloroketone XXII); the corresponding bromoketone may also be prepared and employed as described therein) followed by reduction, to give the asymmetric amino diol XXIII. Optionally, the groups Q<sup>1a</sup> and Q<sup>1b</sup> may be sequentially removed and the resulting amines coupled to N-protected amino acids or peptide chains to give the compound XXV. Where Q<sup>3</sup> is hydrogen, the central amine to which it is bonded may optionally be protected as described above.

Such compounds as are prepared above may also be prepared by employing Methods (B) or (C) of Reaction Scheme 3 using procedures analogous to those of Reaction Scheme 2. In particular, Method (B) of Reaction Scheme 3 may be carried out by procedures analogous to those of Method (E) of Reaction Scheme 2; Method (C) of Reaction Scheme 3 may be carried out by procedures analogous to those of Method (F) of Reaction Scheme 2. The asymmetrical diols XXVI and XXIII may optionally be deprotected and coupled as described above. Where Q<sup>3</sup> is hydrogen, the central amine group to which it is bonded may, in each case, be optionally protected as described above.

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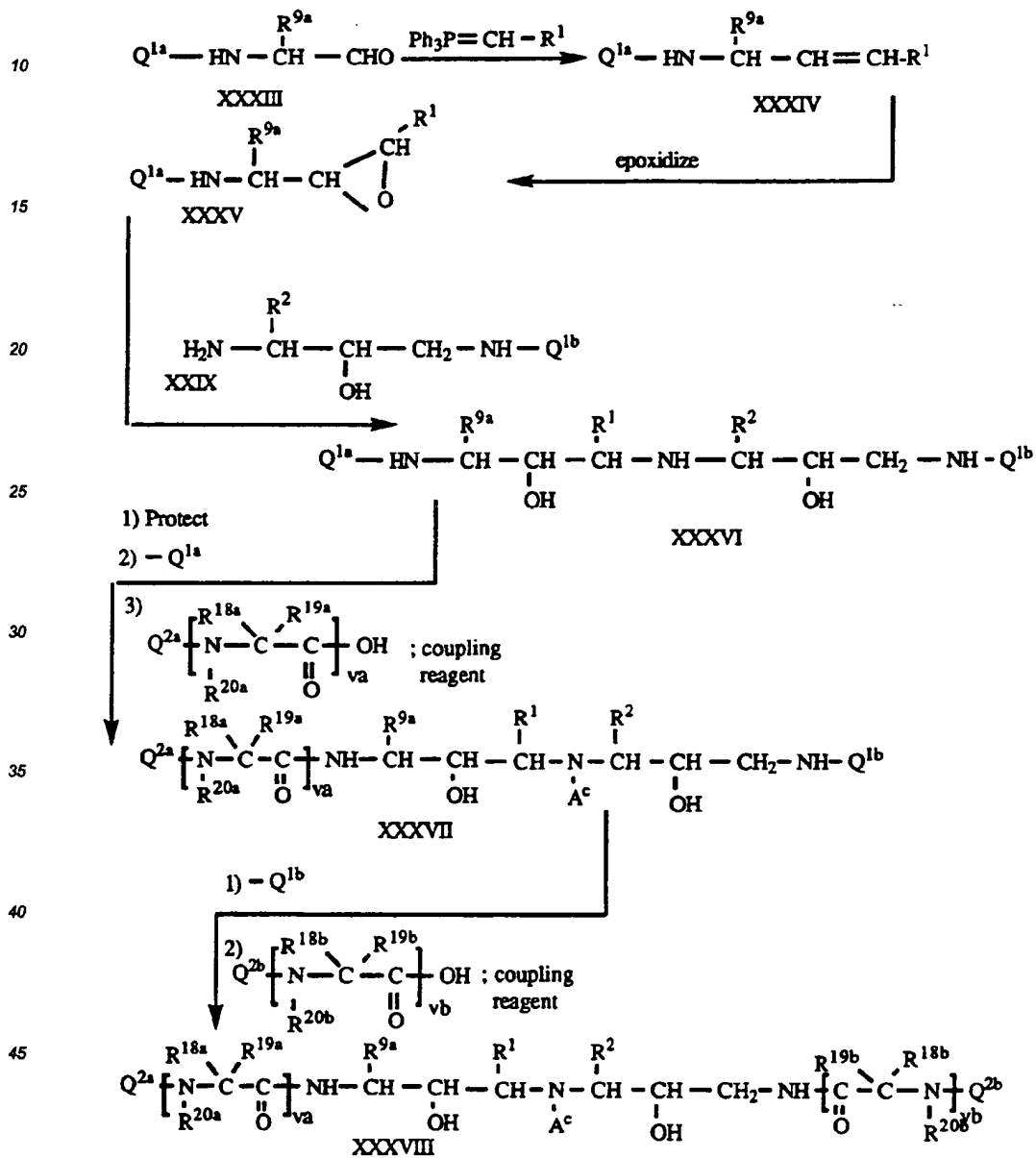
Reaction Scheme 4  
Preparation of Compounds I where R<sup>1</sup>  
and/or R<sup>2</sup> ≠ Hydrogen

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Method (A)

## Reaction Scheme 4 (Cont'd)

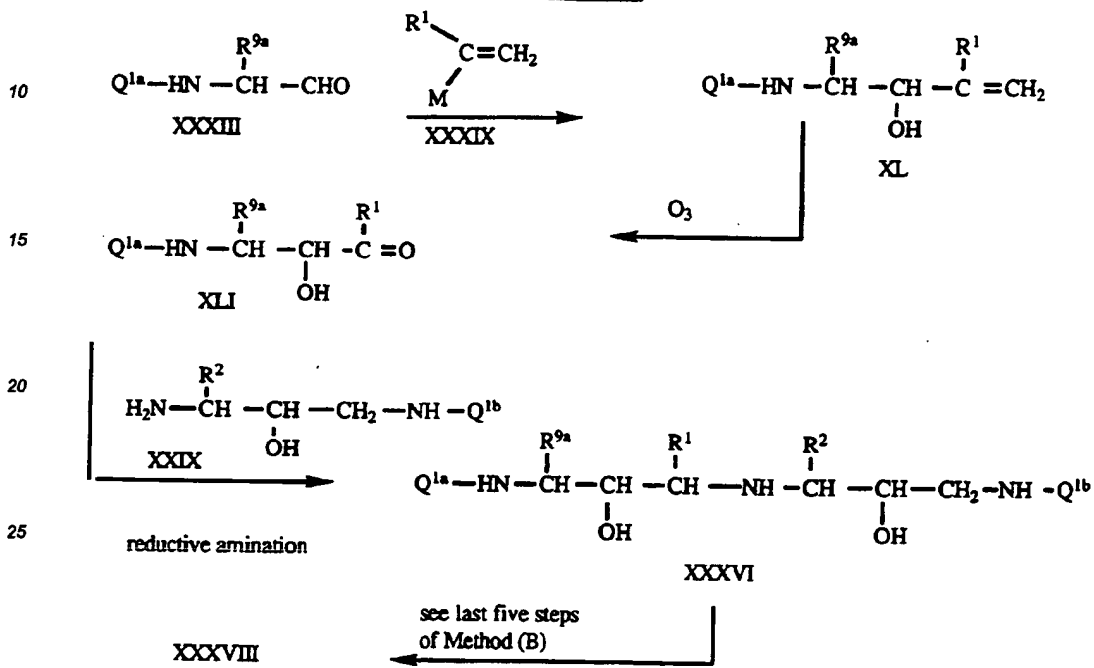
## Method (B)



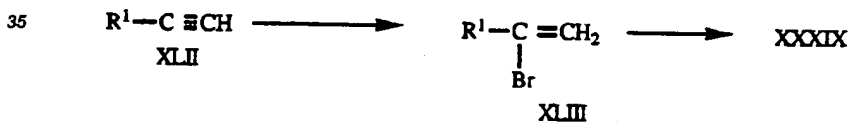
## Reaction Scheme 4 (Cont'd)

5

## Method (C)



## Preparation of Reagent XXXIX:

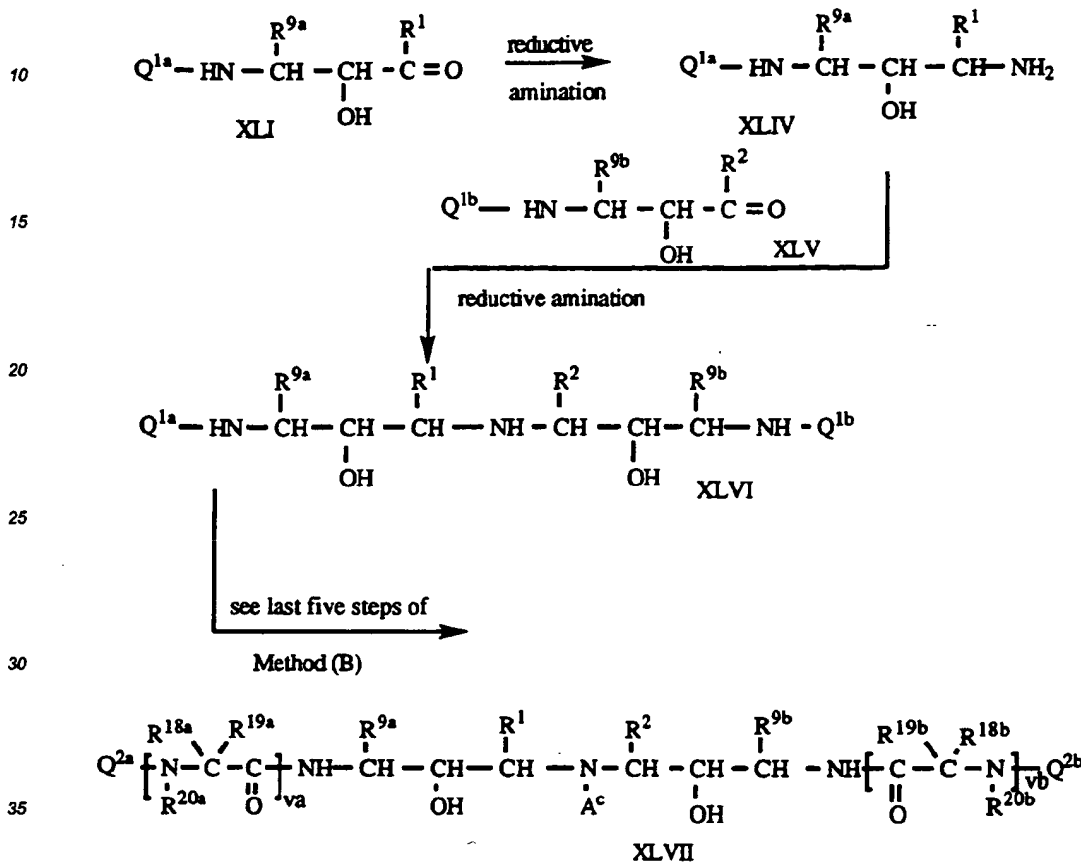




## Reaction Scheme 4 (Cont'd)

5

## Method (D)



40 Reaction Scheme 4 above illustrates Methods (A) to (D) which may be used to prepare compounds of the formula I where R<sup>1</sup> and/or R<sup>2</sup> are not hydrogen.

45 As shown above in Method (A), selective removal of the protecting group (Pro) of compound XXVIII (which compound may be prepared by methods analogous to those employed in the preparation of compound XIII described above) is conducted, where (Pro) is independently chosen from those groups defined for Q<sup>1</sup>, followed by coupling of the resulting amine XXIX with epoxide VI, or chloroketone IV (or corresponding bromoketone) followed by reduction, giving the aminediol XXX. Optionally, where A<sup>c</sup> is hydrogen, the central amine group to which it is bonded may be protected as described above, and the Q<sup>1a</sup> and/or Q<sup>1b</sup> N-terminal groups may then be sequentially or simultaneously removed and the resulting amines coupled to N-protected amino acids or peptide chains by methods described above.

50 Alternatively, as shown in Method (B), the aldehyde XXXIII (see Method (B) of Reaction Scheme 1 for preparation) may be converted to the olefin XXXIV by Wittig or Peterson methodology, and the olefin XXXIV in turn epoxidized by methods analogous to those described above (see Reaction Scheme 1, Method (B)) to yield compound XXXV. The epoxide XXXV may be coupled with the amine XXIX to give the aminediol XXXVI, which optionally may be protected at the central amine when A<sup>c</sup> is hydrogen as described above, and the Q<sup>1a</sup> and/or Q<sup>1b</sup> N-terminal groups may be sequentially or simultaneously deprotected and coupled to N-protected amino acids or peptide chains to give aminediol XXXVIII.

55 The aminediol XXXVIII may also be prepared as shown in Method (C) by reaction of the aldehyde XXXIII with the vinyl organometallic reagent XXXIX, where M is a metal-containing moiety such as magnesium bromide, lithium, CCl<sub>2</sub>, and the like, to give the allylic alcohol XL. The double bond may then be oxidatively cleaved by methods described above to give the ketone XLI, which can then undergo reductive amination in

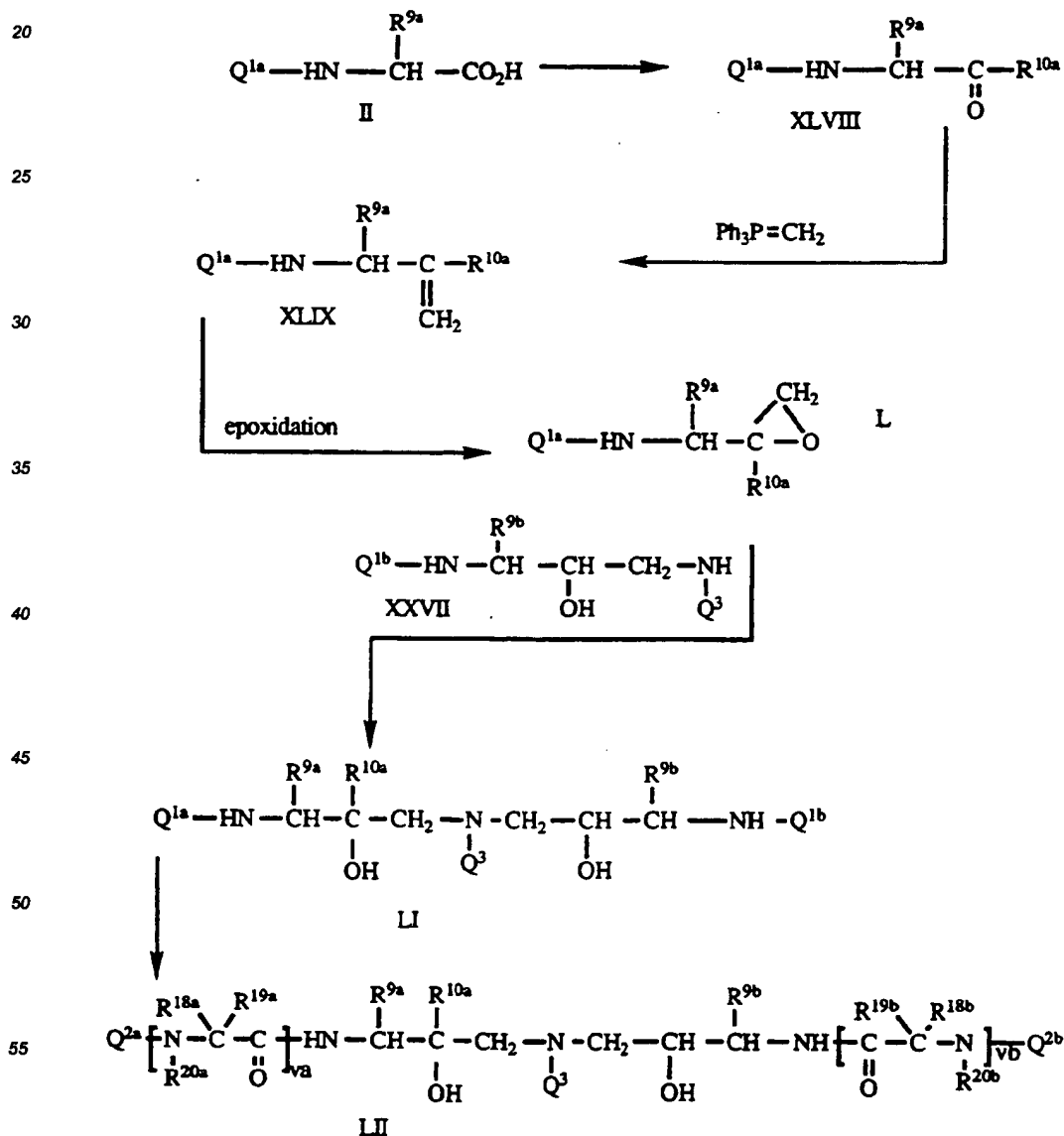
th pr s nce f the amine XXIX, by methods also described above, to give compound XXXVI. Th compound XXXVI may be converted to the amin diol XXXVIII by th m thods described above in Method (B). Th reagent XXXIX employed above in M thod (C) may be prepared from the corresponding acetylene XLII via the vinyl bromide XLIII (Pollet et al., Syn. Commun., 10, 805 (1980); Suzuki et al., Tetrah ron Lett., 24, 731 (1983)).

Alternatively, as shown in Method (D), the ketone XLI may undergo reductive amination by methods described above, in the presence of ammonia, to give the aminoalcohol XLIV, which in turn can undergo reductive amination in the presence of the ketone XLV (see Method (C) for a method for preparation thereof) to give the aminediol XLVI. The aminediol XLVI may then be optionally protected, and sequentially deprotected and coupled to N-protected amino acids or peptide chains as described above in Method (B) to give compound XLVII.

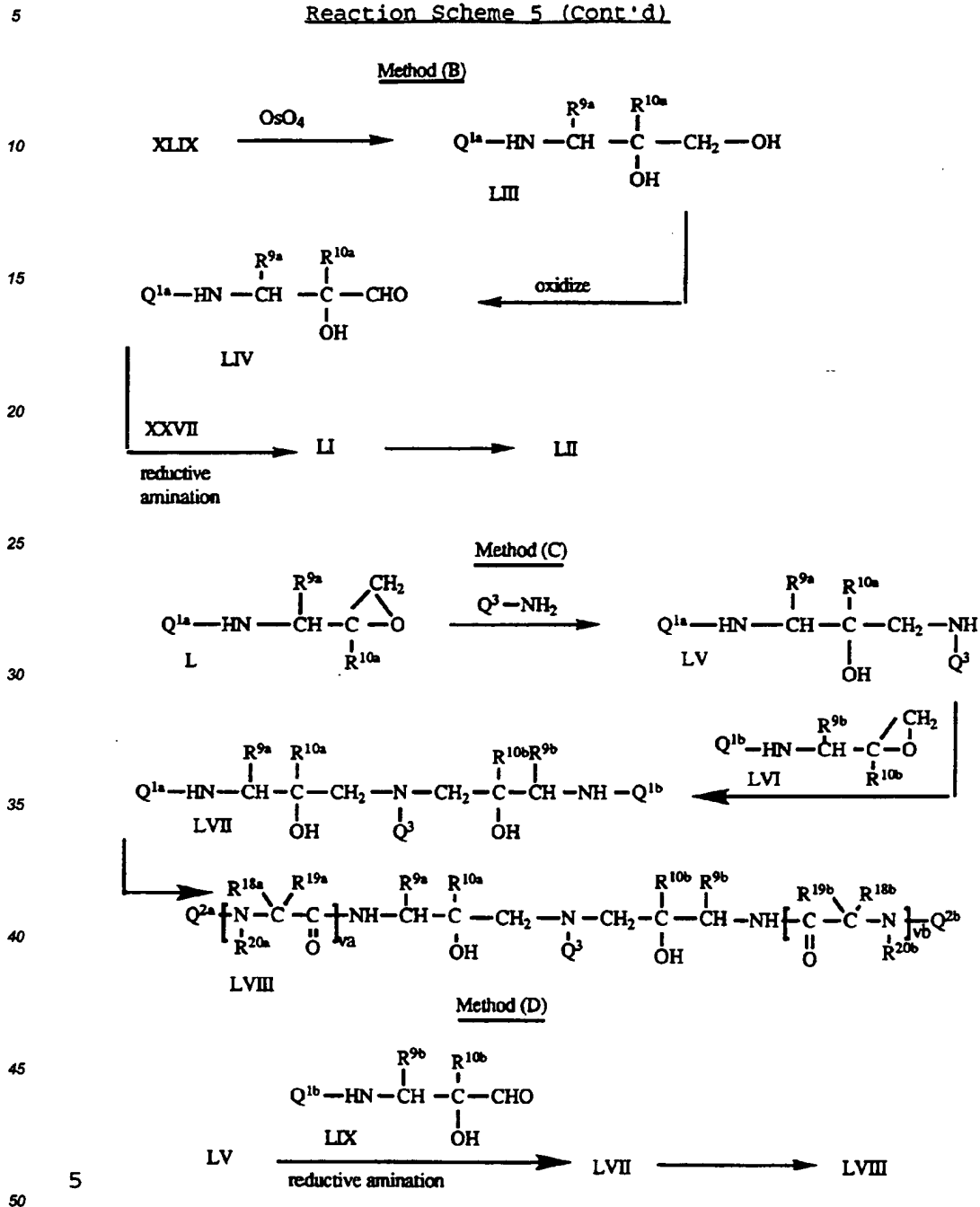
### Reaction Scheme 5

#### Preparation of Compounds I where $R^{10} \neq \text{Hydrogen}$

##### Method (A)



## Reaction Scheme 5 (Cont'd)



Reaction Scheme 5 above illustrates Methods (A) to (D), which may be used to prepare compounds of the formula I where R<sup>10</sup> is not hydrogen.

In Method (A), the protected amino acid II can be converted to the ketone XLVIII by methods known in the art (see, e.g., Gordon et al., Tetrahedron Lett., 28, 1603 (1987)). For example, conversion of amino acid II to an intermediate pyridyl ester or methyl hydroxamate (Wineb et al., Tetrahedron Lett., 22, 3815 (1981)) (not shown), followed by reaction with an organolithium or organomagnesium reagent provides XLVIII. The

ketone obtained may then be converted to the olefin XLIX via a Wittig or Peterson reaction, which can be followed by epoxidation using methods as described above. The epoxide L so formed may be coupled with the aminoalcohol XXVII to give the aminediol LI. Optionally, the Q<sup>1</sup> groups may then be sequentially or simultaneously deprotected and coupled to N-protected amino acids or peptide chains using methods as described above to give compound LII.

Alternatively, as shown in Method (B), the olefin XLIX may be converted directly to the cis diol LIII using osmium tetroxide or potassium permanganate (Kochi et al., Metal Catalyzed Oxidations of Organic Compounds, pp. 162 - 171, 294 - 296, Academic Press (1981)), and the diol LIII in turn oxidized to the aldehyde LIV by methods described above. The aldehyde LIV may then undergo reductive amination in the presence of the aminoalcohol XXVII to give the aminediol LI, and the latter compound converted to the aminediol LII, by methods described above.

Another route is shown in Method (C). In Method (C), the epoxide L may be coupled to a primary amine or ammonia Q<sup>3</sup>-NH<sub>2</sub> by methods described above to give the aminoalcohol LV, which can be coupled to the epoxide LVI (see Method (A) for preparation thereof), to give the aminediol LVII. As described above, the Q<sup>1</sup> protecting groups may optionally be sequentially or simultaneously removed and the resulting amino groups coupled to N-protected amino acids or peptide chains to give compound LVIII.

Alternatively, as shown in Method (D), the aminoalcohol LV may undergo reductive amination in the presence of the aldehyde LIX (see Method (B) for preparation) by methods described above to give compound LVII, and the latter converted to compound LVIII by methods also described above, for example, in Method (C).

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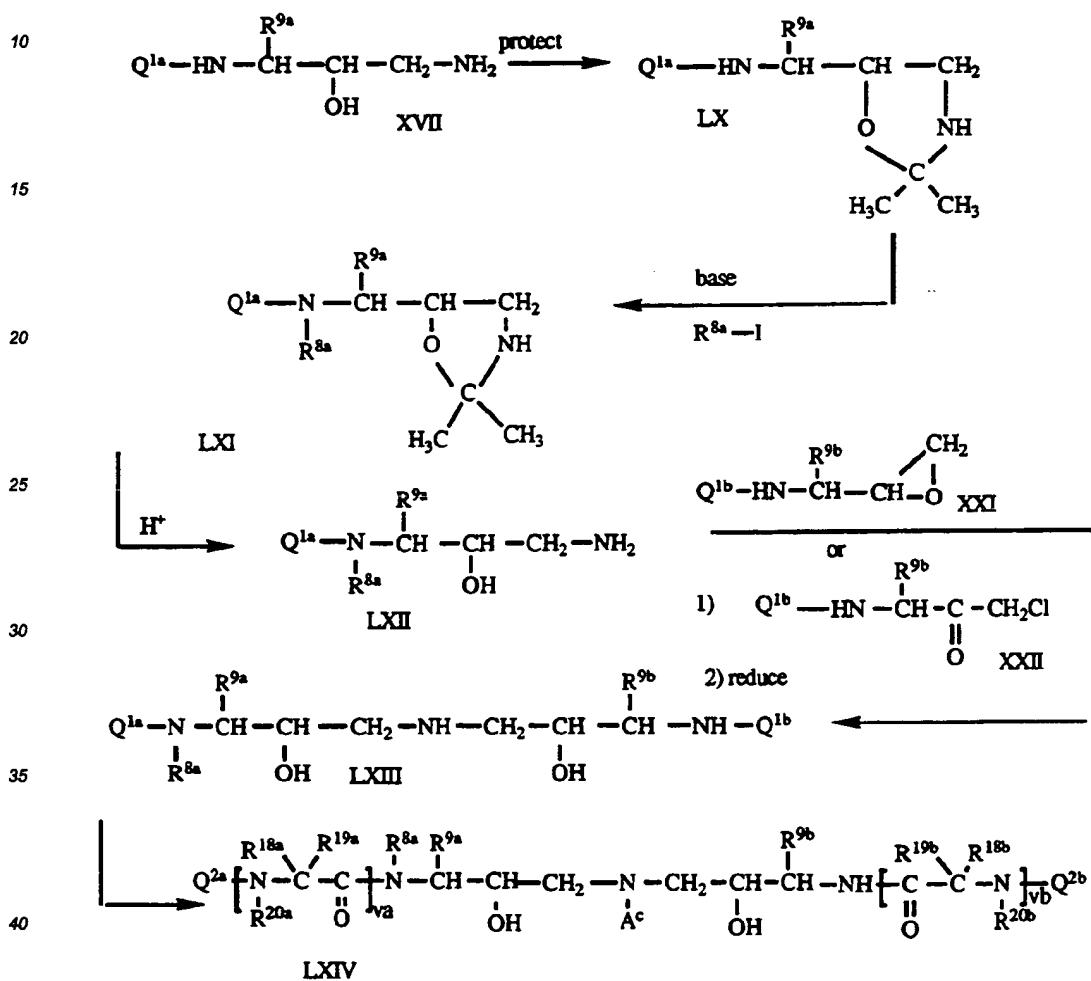
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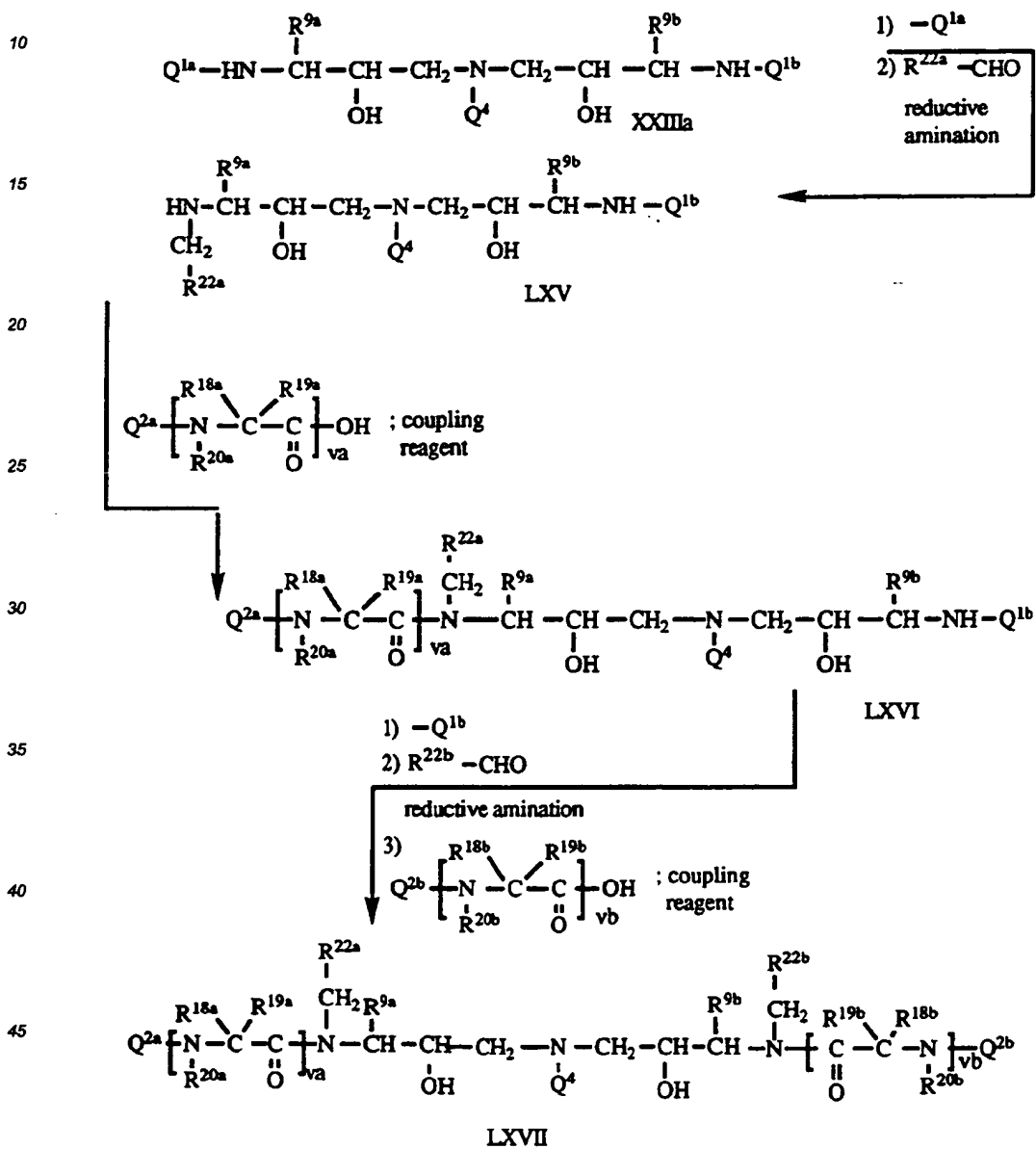
## Reaction Scheme 6

Preparation of Compounds I where  $R^8 \neq \text{Hydrogen}$ 

## Method (A)

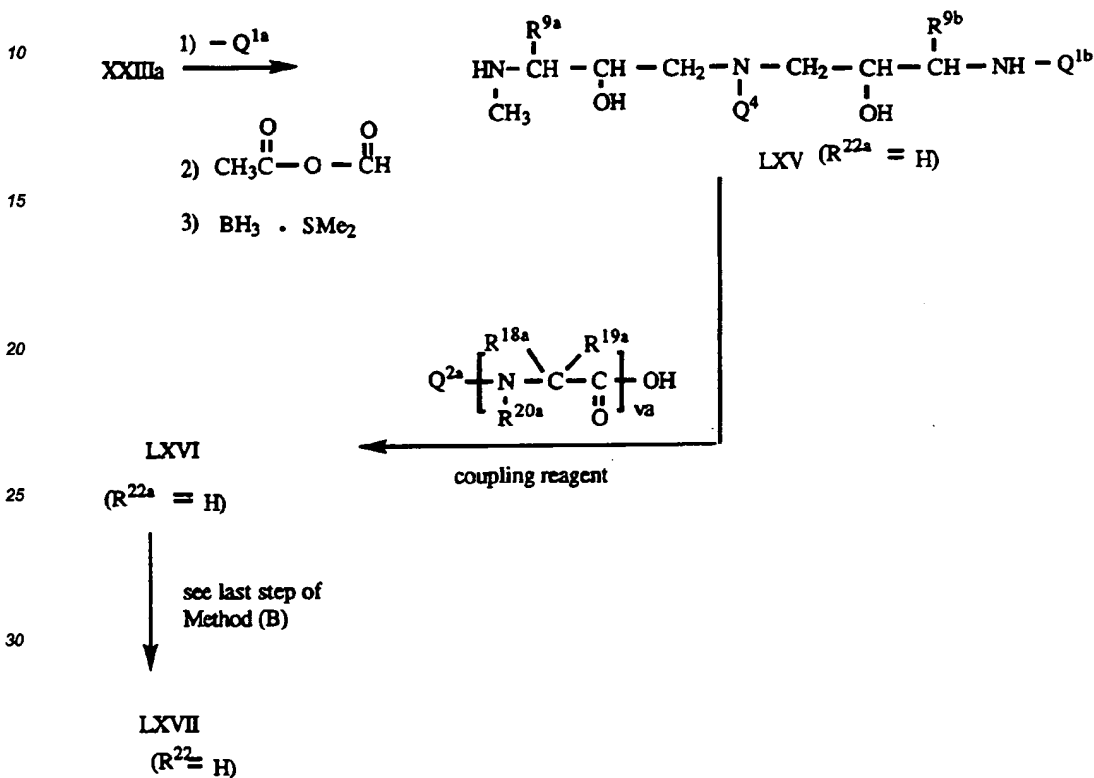


## Reaction Scheme 6 (Cont'd)

Method (B) ( $R^{8a}$  is  $-\text{CH}_2\text{R}^{22a}$ ;  $R^{8b}$  is  $-\text{CH}_2\text{R}^{22b}$ )

## Reaction Scheme 6 (Cont'd)

5

Method (C) ( $R^8 = CH_3$ )

Reaction Scheme 6 above illustrates Methods (A), (B) and (C) which may be used to prepare compounds of the formula I where  $R^8$  is not hydrogen.

In Method (A), the aminoalcohol XVII can be protected as shown yielding compound LX (Bergmann, Chem. Rev., 53, 309 (1953)) and the non-basic nitrogen alkylated (Benoit et al., Can. J. Chem., 49, 1968 (1971)) by treatment with a base such as sodium or potassium hydride, sodium or potassium hexamethyldisilazide, or the like, followed by, for example, an alkylating agent such as an alkyl iodide, bromide, chloride, tosylate, triflate, or the like.  $Q^{1a}$  is an activating group which renders the hydrogen on the nitrogen atom to which it is bonded acidic and easily removed with a base as described above, such as a group forming, together with  $-N(R^{8a})$ , a carbamate or amide group. The aminoalcohol LXI formed can then be deprotected to form compound LXII, and the latter coupled to an epoxide XXI, or to a chloroketone XXII (the corresponding bromoketone may be employed as described above) followed by reduction, by methods described above to give an aminediol LXIII, which optionally may be protected at the central amine and the  $Q^1$  groups sequentially or simultaneously deprotected and coupled to N-protected amino acids or peptide chains to give LXIV.

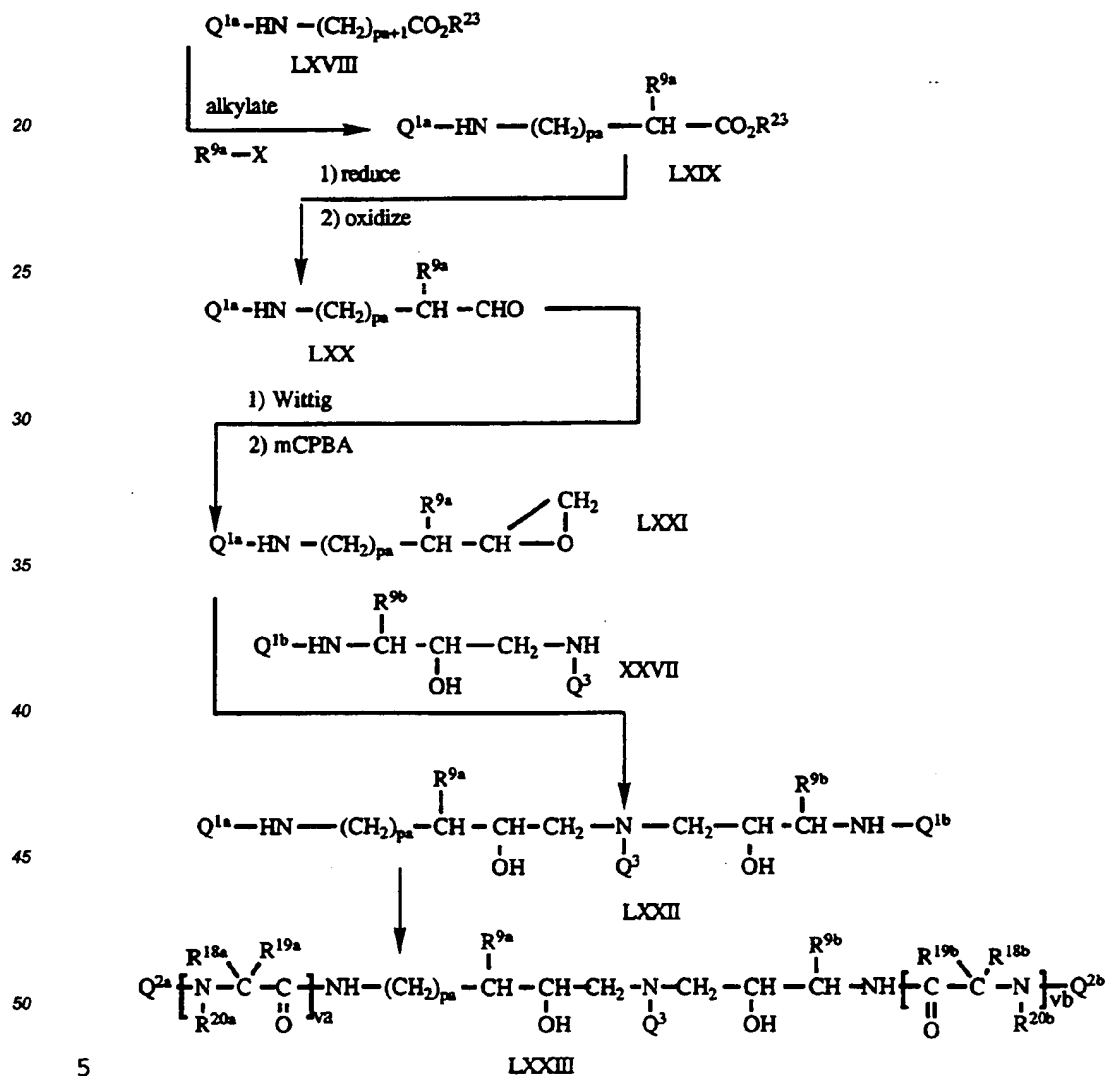
Alternatively, as shown in Method (B), an aminediol such as XXIIIa (which may be prepared from aminediol XXIII by methods known to one of ordinary skill in the art) may be monodeprotected at  $Q^{1a}$  or  $Q^{1b}$  and the resulting amine reacted under reductive amination conditions in the presence of a compound of the formula  $R^{22a}-CHO$  where  $R^{22a}$  is hydrogen or alkyl, by methods described above to give LXV.  $Q^4$  is defined to include alkyl and thos groups includ d in th definition of  $Q^1$ . The resulting amin may be optionally coupled by methods d scribed abov to give compound LXVI. A similar process may optionally b carried out at the other nd of the molecule to produce an aminediol such as LXVII.

In Method (C), compounds where  $R^8$  is a methyl group may be prepared by d protecting an aminediol XXIIIa, where  $Q^4$  is not formyl; formylating th deprotect d amine; and reducing th resulting formamide to

the methylated amine using a triethylamine-dimethyl sulfide complex (Krishnamurthy, Tetrahedron Lett., 23, 3315 (1982)). The methylated amine LXV ( $R^{22a} = H$ ) may optionally be coupled to an N-protected amino acid or peptide chain to give the compound LXVI ( $R^{22a} = H$ ), and the compound LXVI converted to compound LXVII ( $R^{22} = H$ ) as described above.

Reaction Scheme 7  
Preparation of Compounds I where  
p and/or q  $\neq$  zero

Method (A)



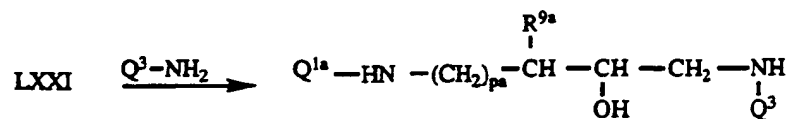


Reaction Scheme 7 (Cont'd)

5

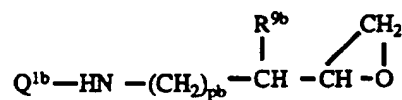
Method (B)

10



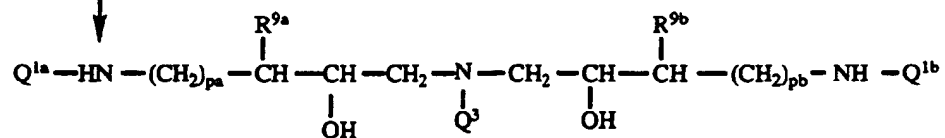
LXXIV

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LXXV

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LXXVI

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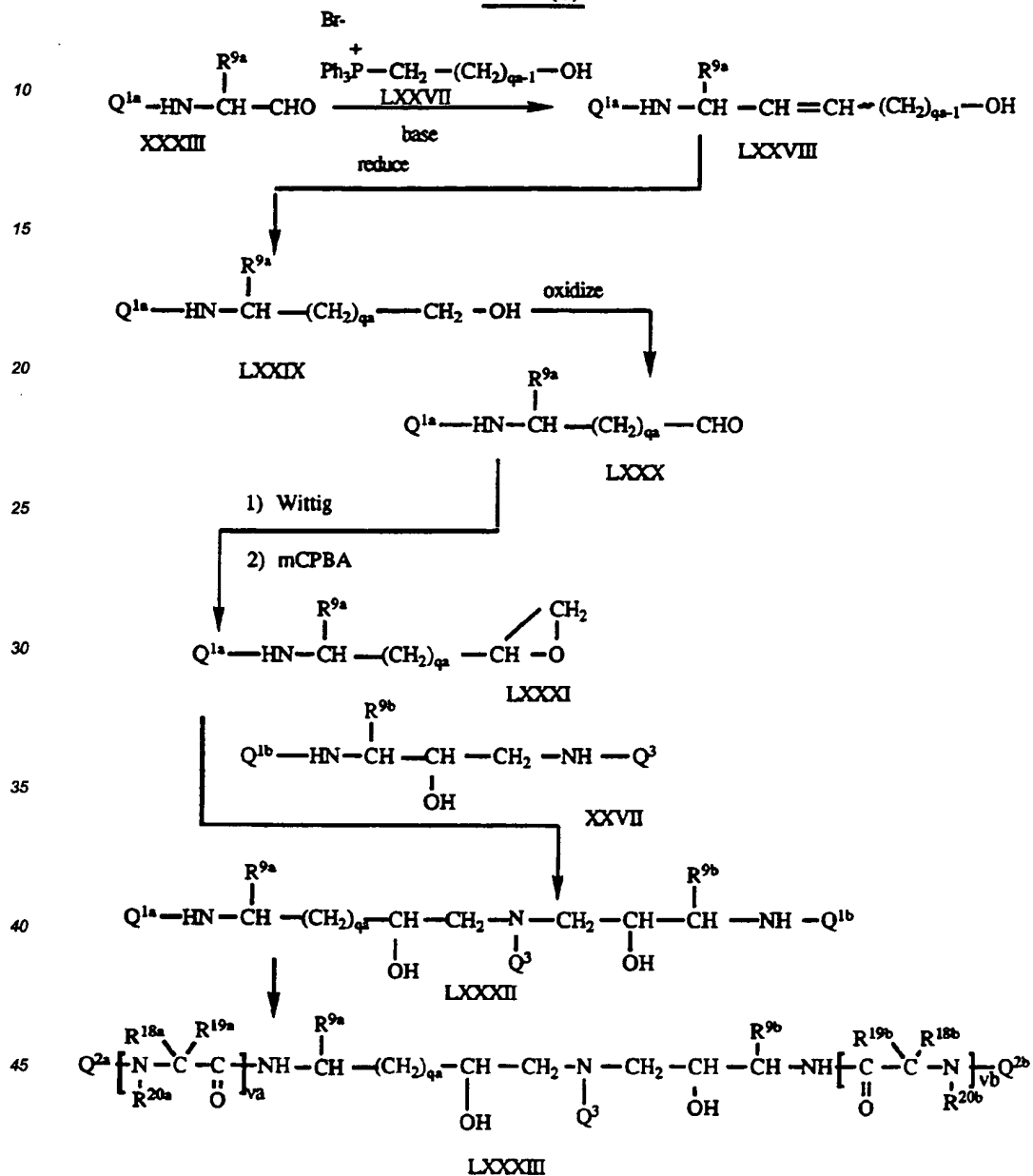
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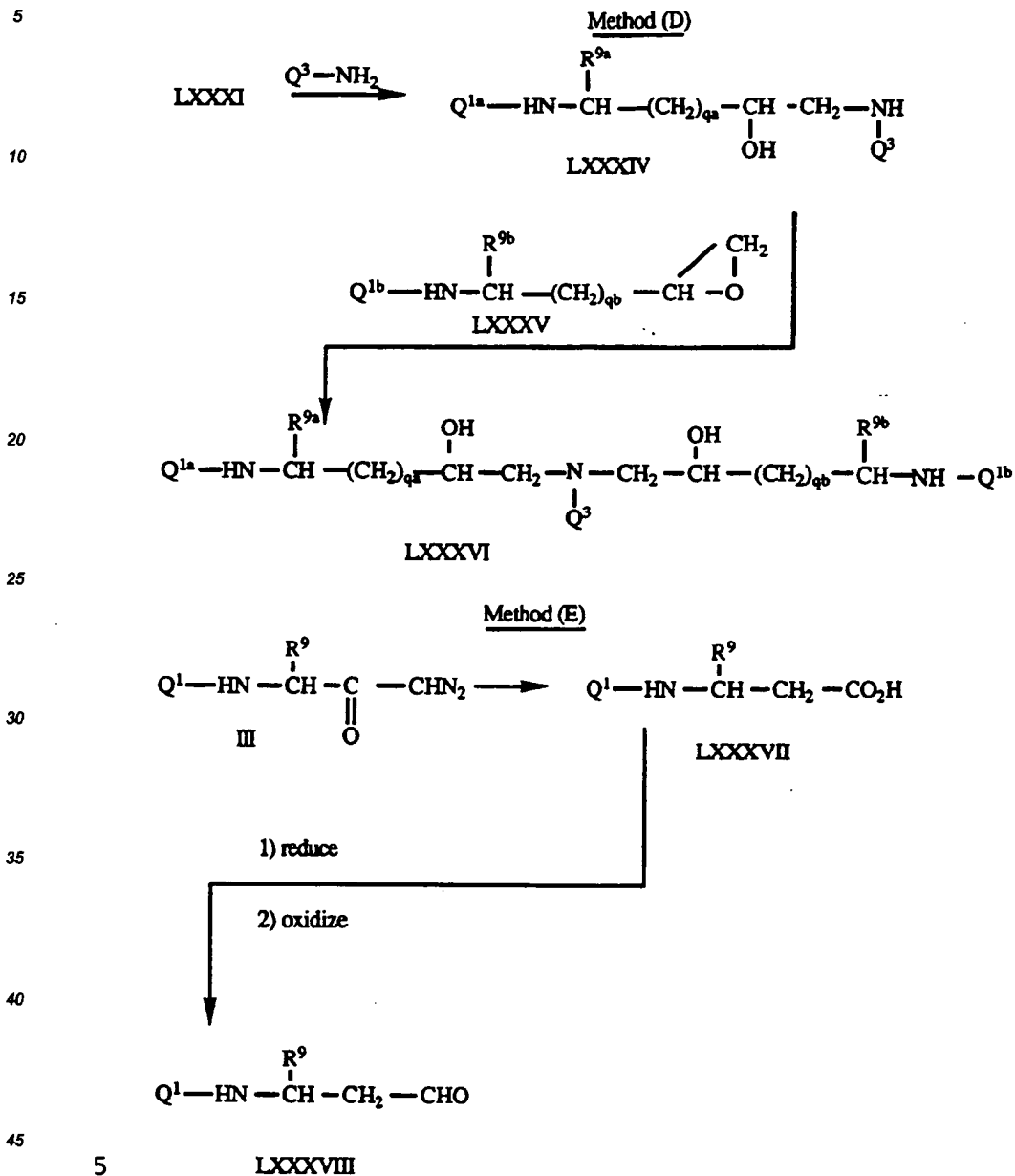
## Reaction Scheme 7 (Cont'd)

5

## Method (C)



Reaction Scheme 7 (Cont'd)



Reaction Scheme 7 above illustrates Methods (A) to (E), which may be used to prepare compounds of the  
50 formula I where p and/or q are not zero.

In Method (A), the protected amino ester LXVIII ( $R^{23}$  may be unsubstituted lower alkyl, aryl or aryl-lower alkyl) where  $p_a = 1-4$  and  $q = 0$  can be alkylated via its enolate anion (formed by treatment of the ester with a base such as lithium diisopropylamide, lithium bis(trimethylsilyl)amide or the like) with  $R^{2a} - X$ , where  $X$  is halogen, tosylate, mesylate or the like to give the ester LXIX. The ester may be reduced directly to the aldehyde LXX with diisobutylaluminum hydride or in two steps by conversion to the primary alcohol with a hydride reducing agent and then oxidation to the aldehyde as described above. The aldehyde can be converted directly to the epoxid LXXI via reaction with a sulfonium or arsonium ylide or by a Wittig or Peterson reaction to give the corresponding olefin (not shown), followed by epoxidation as described above. The epoxid may be coupled to the amino alcohol XXVII to give the aminediol LXXII, which optionally may then be sequentially or simultaneously

multaneously deprotected and coupled to N-protected amino acids or peptide chains as described above to give the compound LXXIII. The starting ester LXXVIII of Method (A) may be obtained by methods known to those skilled in the art such as those methods described in J. March, "Advanced Organic Chemistry", John Wiley (1985) (see pages 1157 - 1158).

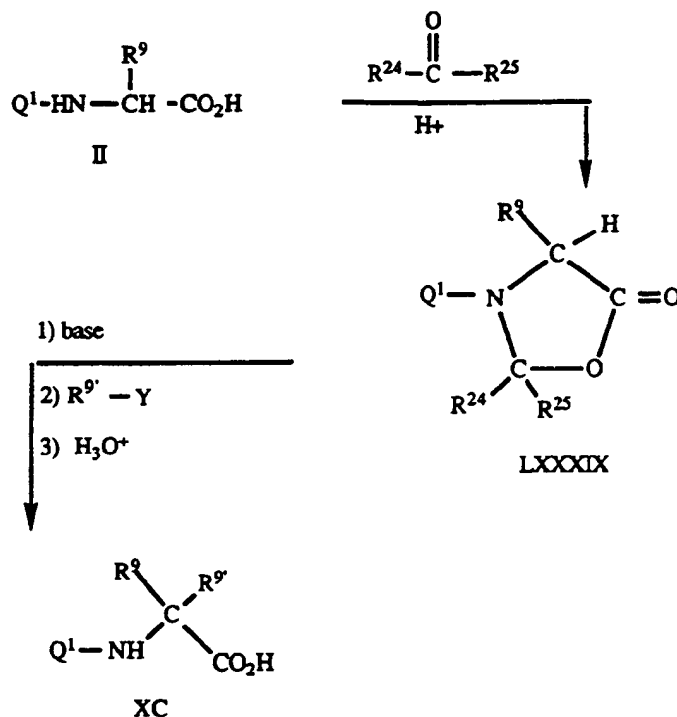
Method (B) illustrates a method for obtaining compounds where both  $p_a$  and  $p_b > 0$ . In this method, the epoxide LXXI is reacted with ammonia or a primary amine  $Q^3-NH_2$  to give the compound LXXIV, followed by coupling with the epoxide LXXV (which may be prepared by a method analogous to that for preparing the epoxide LXXI above) to give compound LXXVI. The compound LXXVI may optionally then be sequentially or simultaneously deprotected and coupled to N-protected amino acids or peptide chains as described above.

Method (C) illustrates a method for obtaining compounds where  $q_a = 2-4$  and  $p = 0$ . In Method (C), Wittig reaction of the hydroxyphosphorane LXXVII with the protected amino aldehyde XXXIII gives the olefin LXXVIII which can be reduced to the saturated alcohol LXXIX under catalytic hydrogenation conditions. Oxidation of the alcohol LXXIX to the aldehyde LXXX may be followed by conversion to the epoxide LXXXI, the latter achieved by a Wittig reaction followed by treatment with *m*-chloroperoxybenzoic acid (mCPBA). The epoxide LXXXI is then coupled with the amino alcohol XXVII to give the aminediol LXXXII as described above. The aminediol may then optionally and sequentially be deprotected and coupled to N-protected amino acids or peptide chains to give compound LXXXIII. The hydroxyphosphorane starting material LXXVII may be prepared by reaction of the appropriate haloalcohol with triphenylphosphine under standard conditions.

Method (D) illustrates a method where compounds in which  $q_a$  and  $q_b$  are both  $>1$  and  $p = 0$  may be prepared by reaction of the epoxide LXXXI with ammonia or a primary amine  $Q^3-NH_2$  to give compound LXXXIV. The latter compound may then be coupled with the epoxide LXXXV (prepared, e.g., by the method employed above for preparation of the epoxide LXXXI) to yield the aminediol LXXXVI. The aminediol LXXXVI may optionally then be sequentially or simultaneously deprotected and coupled to N-protected amino acids or peptide chains as described above.

Method (E) illustrates a method for preparing intermediate compounds which may be employed in preparing aminediols where  $q = 1$  and  $p = 0$ . In Method (E), the intermediate aldehyde LXXXVIII may be prepared by an Arndt-Eistert reaction (Meier and Zeller, *Angew. Chem. Int. Ed. Engl.*, **14**, 32 (1975)) on the diazoketone III to give the carboxylic acid LXXXVII. Conversion of the carboxylic acid to the aldehyde may be conducted by reduction and oxidation as described above. The aldehyde may then be converted to the desired aminediol as described in Methods (C) and (D).

## Reaction Scheme 8

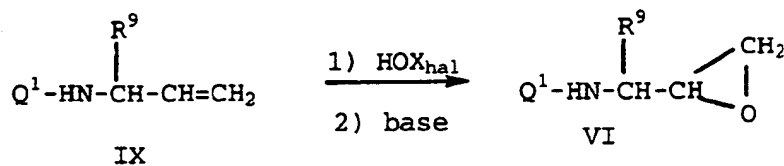
Preparation of Compounds I where  $R^{9'} \neq \text{Hydrogen}$ 

Reaction Scheme 8 illustrates a method for the preparation of compounds of the formula I where  $R^9$  is not hydrogen.

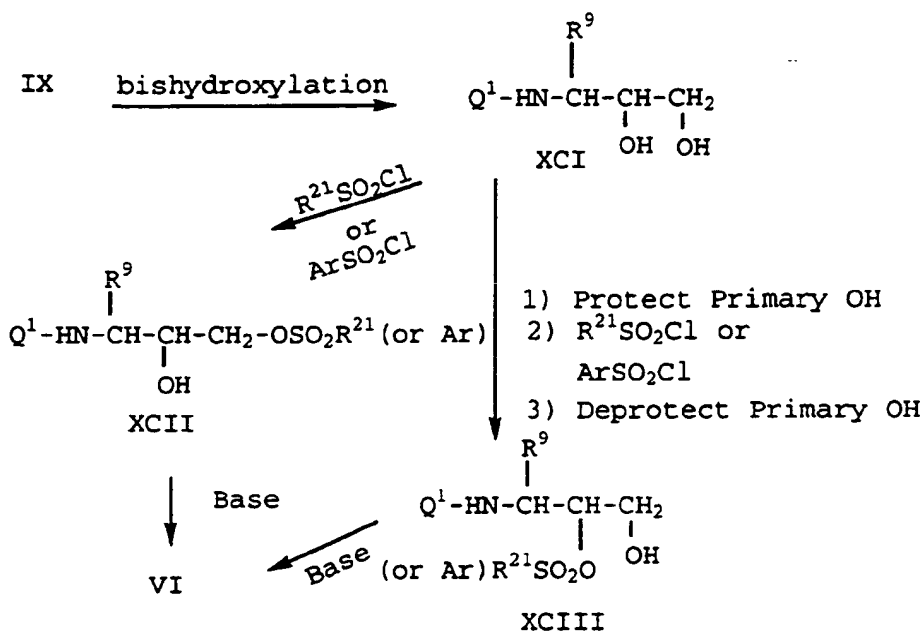
An N-protected amino acid II may be converted into an acetal LXXXIX where  $R^{24}$  and  $R^{25}$  are independently hydrogen or unsubstituted lower alkyl as shown. Treatment of the acetal LXXXIX with a base such as lithium diisopropyl amide, followed by reaction with a compound  $R^{9'}\text{-Y}$  where Y may be Cl, Br, I or triflate, and hydrolysis of the acetal gives the  $\alpha$ -substituted amino acid XC. The amino acid XC may be converted to amine diols of the formula I by those methods described in Schemes 1 to 7 above. Unnatural, optically active  $\alpha$ -amino acids can be prepared by methods such as those described in Evans et al., *J. Am. Chem. Soc.*, 112, 4011 (1990); and Oppolzer et al., *Tetrahedron Lett.*, 30, 5603, 6009 (1989). Alternative methods are also described in Williams, R. M., *Synthesis of Optically Active  $\alpha$ -Amino Acids*, Pergamon Press: Oxford (1989).

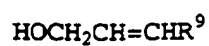
Reaction Scheme 9  
Alternative Methods for  
Preparation of Intermediate Materials

Method (A)

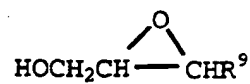


Method (B)



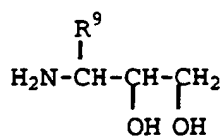
Method (C)

asymmetric  
epoxidation

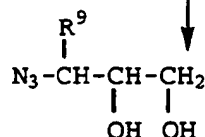


XCIV

XCV



reduce

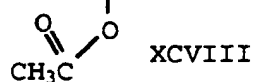
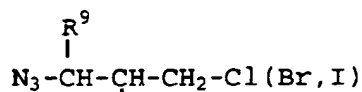
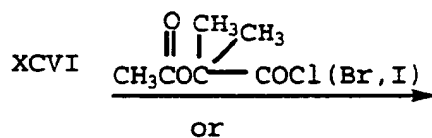


XCVI

XCVII

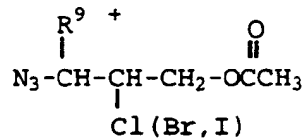
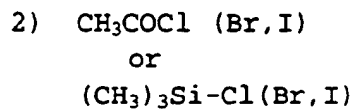
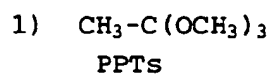
+Q<sup>1</sup>

XCI

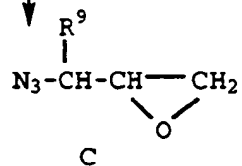
Method (D)

XCVIII

Base

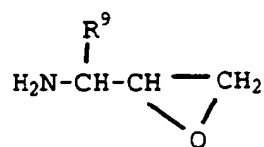


XCIX



C

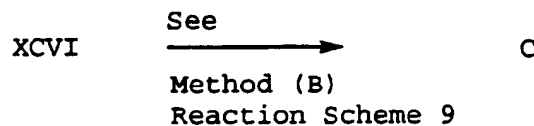
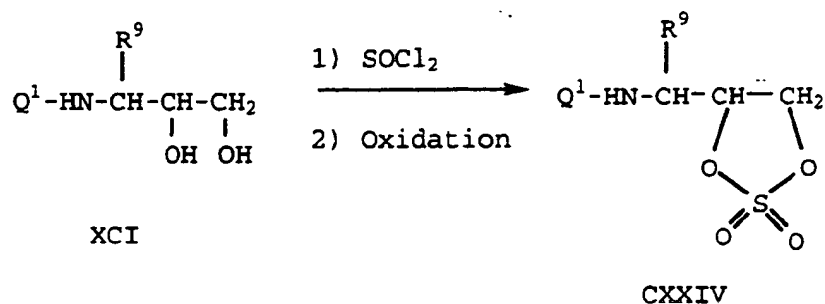
reduce



CI

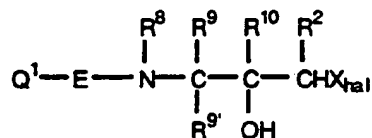
+ Q<sup>1</sup>

VI

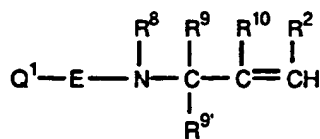
Method (E)Method (F)

Intermediate materials for the preparation of compounds of the formula I may alternatively be prepared by Methods (A) to (F) as shown in Reaction Scheme 9 above.

In this regard, the present invention provides a novel method for the preparation of a halohydrin of the following formula:



where  $\text{Q}^1$ , E,  $\text{R}^2$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{9'}$  and  $\text{R}^{10}$  are as defined above, particularly where  $\text{R}^9$  is not the same as  $\text{R}^{9'}$  (most preferably, where one of  $\text{R}^9$  or  $\text{R}^{9'}$  is hydrogen), and  $\text{X}_{\text{hal}}$  is chloro or bromo, comprising the step of contacting an olefin of the following formula:



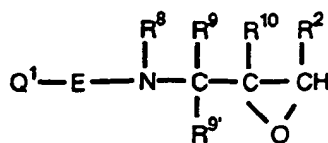
with the compound  $\text{HOX}_{\text{hal}}$ .

The compound  $\text{HOX}_{\text{hal}}$  may be formed *in situ* for use in the method of the present invention, such as by contacting N-chlorosuccinimide, N-bromosuccinimide,  $\text{Br}_2$  or  $\text{Cl}_2$  with water. Preferred molar ratios of the compound  $\text{HOX}_{\text{hal}}$  to the olefin starting material are from about 1:1 to about 3:1.

In a preferred embodiment, the novel method of the present invention comprises the optional further step of preparing an epoxide of the following formula:



5



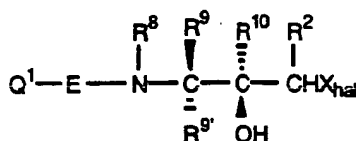
by contacting the above halohydrin with a base.

10 The base employed may be any basic compound providing conversion of the halohydrin to the epoxide, such as alkali metal (e.g., sodium or potassium) hydroxides, alkali metal (e.g., sodium or potassium) hydrides, alkali metal (e.g., sodium or potassium) carbonates, or amine bases (e.g., trialkylamines). Preferred molar ratios of the base to the halohydrin are from about 1:1 to about 5:1.

15 The temperature employed during the above steps for halohydrin and, optionally, epoxide formation is preferably from about -78°C to about 50°C. The steps are preferably conducted in an organic solvent such as dioxane or tetrahydrofuran. An alcohol (for example, methanol) is preferably employed during epoxide formation, such as by addition to the aforementioned organic solvent when a single pot is employed, particularly where the base is other than an amine base. Times employed are those sufficient for halohydrin and, optionally, epoxide formation.

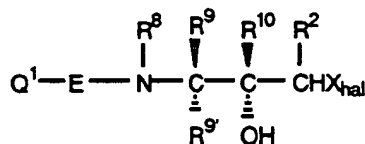
20 The above novel method of the present invention preferentially (that is, in a greater than 1:1 molar ratio) provides halohydrins of the following relative stereoconfiguration:

25



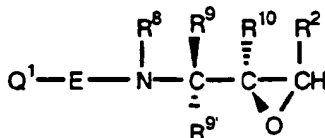
30 relative to the corresponding stereoisomers thereof:

35



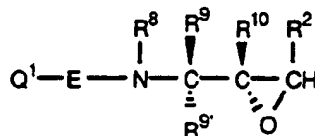
40 Thus, the above method of the present invention comprising the preferred further step of epoxide formation is particularly advantageous where epoxides having the following relative stereoconfiguration are sought:

45



50 as such compounds are formed preferentially (that is, in a greater than 1:1 molar ratio) relative to the corresponding stereoisomers thereof:

55



These starting olefins may be prepared by methods such as those described by Luly et al., *J. Org. Chem.*, **52**, 1487-1482 (1987).

Method (A) illustrates the novel method of the present invention. In Method (A), olefin IX is converted to the halohydrin (not shown) by treatment with aqueous bromine or N-bromosuccinimide or N-chlorosuccinimide, and then treated with base, such as potassium carbonate or potassium or sodium hydroxide or the like to give epoxide VI.

As shown in Method (B), olefin IX may be converted to the diol XCI by treatment with osmium tetroxide or potassium permanganate, or other methods known in the art (Kochi, et al., *Metal Catalyzed Oxidations of Organic Compounds*, pp. 162-171, 294-296, Academic Press (1981); Jacobsen, et al., *J. Am. Chem. Soc.*, **110**, 1968 (1988); Sharpless, et al., *J. Org. Chem.*, **57**, 2768 (1992)). Diol XCI may be treated with a sulfonyl chloride (e.g., methanesulfonyl chloride or p-toluenesulfonyl chloride; Ar denotes aryl) to give the sulfonate XCII; or, alternatively, the primary hydroxyl group of XCI may be selectively protected (see Greene, *Protective Groups in Organic Synthesis*), and the secondary hydroxyl group sulfonylated, followed by deprotection of the primary hydroxyl group, to give XCIII. The sulfonate esters XCII or XCIII may be independently converted to the epoxide VI by treatment with base, such as sodium or potassium hydroxide, or an alkylamine base such as triethylamine; the latter reaction from XCIII occurs with inversion of the configuration of the secondary hydroxyl group.

In Method (C) (see Thompson, et al., *J. Am. Chem. Soc.*, **115**, 801 (1993) and Bennett, et al., *JCS Chem. Commun.*, 737 (1993)), the olefin XCIV may be converted to the epoxide XCV by asymmetric epoxidation (Gao, et al., *J. Am. Chem. Soc.*, **109**, 5765 (1987)). Starting olefin XCIV may readily be prepared by one of ordinary skill in the art by known methods (e.g., Wittig reaction, March, *Advanced Organic Reactions*, pp 839-841 and pp 845-854 (Third Edition)). Epoxide XCV can be converted to the azidodiols XCVI by treatment with azide anion, such as treatment with sodium azide and titanium bisisopropoxide (Caron, et al., *J. Org. Chem.*, **53**, 5185 (1988); Omaka, et al., *Chem. Lett.*, 1327 (1986)). The azidodiols can be reduced by methods described above in Reaction Scheme 2, Method (E) to give the aminodiols XCVII. Protection of the amine by methods known in the art, such as those described in Greene, *Protective Groups in Organic Synthesis*, may provide Compound XCI.

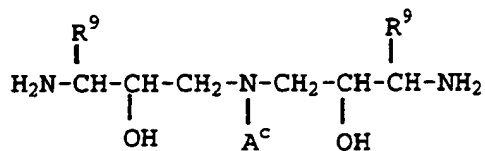
Alternatively, as described in Method (D), azidodiols XCVI may be converted to the mixture of haloacetates XCVIII and XCIX by treatment with 2-acetoxyisobutyryl halide, or treatment with trimethyl orthoacetate and PPTs followed by acetyl halide (e.g., acetyl bromide) or trimethylsilyl halide (e.g., trimethylsilyl chloride) (Russell, et al., *J. Am. Chem. Soc.*, **95**, 4025 (1973); Thompson, et al., *ibid.*, **115**, 801 (1993); Kolb, et al., *Tetrahedron*, **48**, 10515 (1992)). The haloacetates XCVIII and XCIX may be treated with base such as sodium methoxide or sodium or potassium carbonate, to give the azidoepoxide C. Reduction of the azidoepoxide C to the aminoepoxide CI followed by protection of the amine by methods known in the art provides epoxide VI.

Alternatively, as shown in Method (E), the azidodiols XCVI may be converted to the epoxide C by methods analogous to those described above (Reaction Scheme 9, Method (B)).

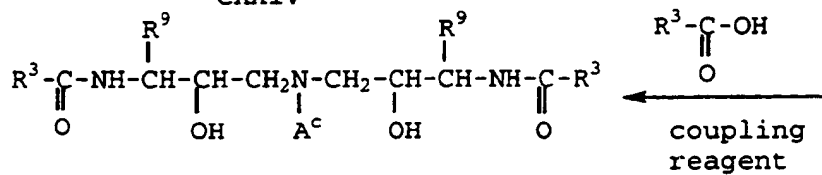
In Method (F), diol XCI may be converted to the cyclic sulfate CXXIV by treatment, first with thionyl chloride to give the cyclic sulfite (structure not shown), and then oxidation with potassium permanganate or ruthenium trichloride/sodium periodate, and the like (Lohray, *Synthesis*, 1035 (1992); Gao, et al., *J. Am. Chem. Soc.*, **110**, 7538 (1988)). Compound CXXIV, or the intermediate sulfite, may be converted to aminediols by methods described above for the conversion of epoxides VI and/or XXI.

Reaction Scheme 10

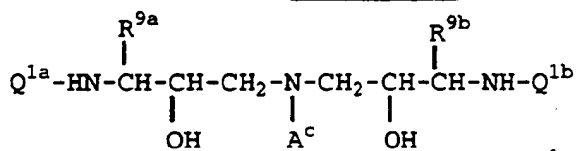
Alternative Methods for  
Preparation of Compounds I where  $A^a = A^b$   
and  $D^a = D^b$

Method (A)

CXXIV



CII

Method (B)

CXXV

CII

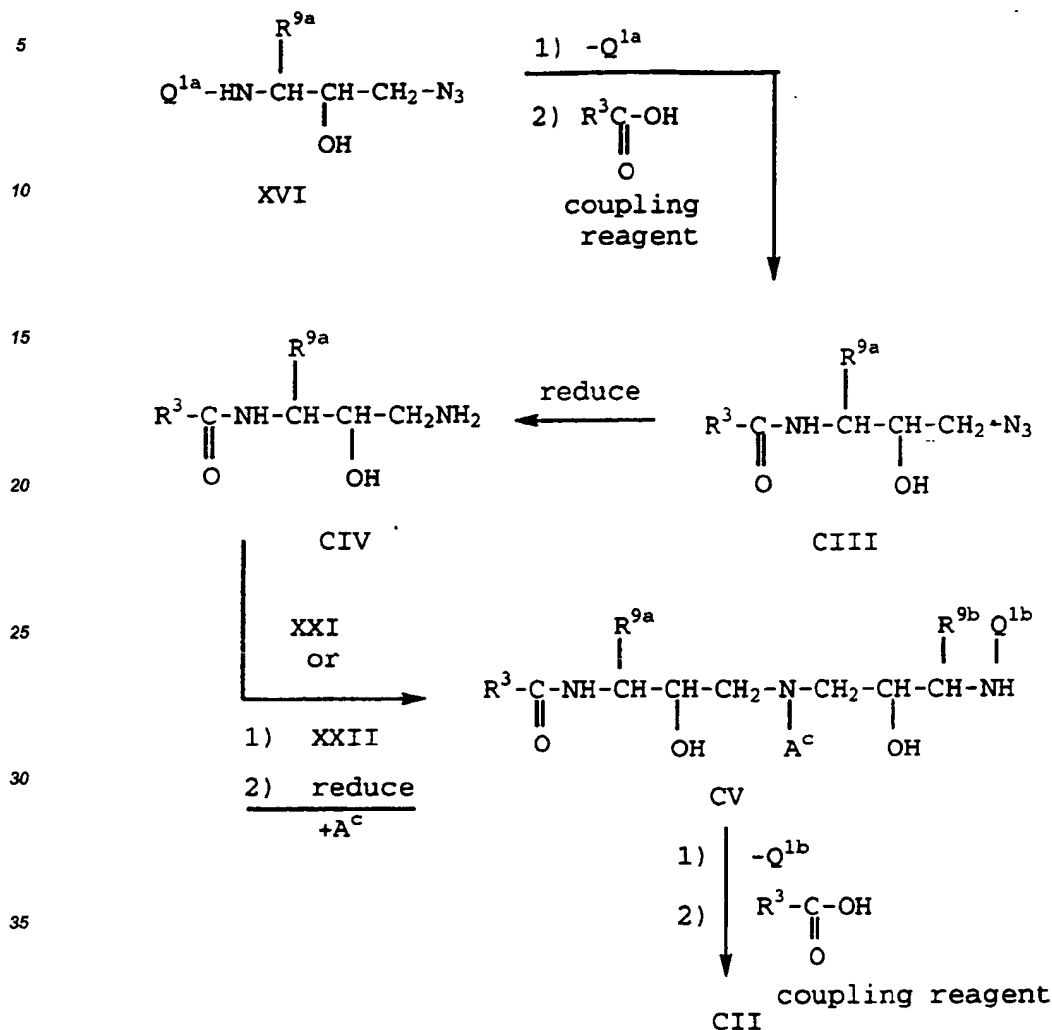
1)  $-\text{Q}^{1a}$ 2)  $\text{R}^3-\text{C}(=\text{O})-\text{OH}$ 

coupling reagent

3)  $-\text{Q}^{1b}$ 4)  $\text{R}^3-\text{C}(=\text{O})-\text{OH}$ 

coupling reagent

## Method (C)



Reaction Scheme 10 above illustrates Methods (A) through (C), which may be used to prepare compounds of the formula I where A<sup>a</sup> is the same as A<sup>b</sup> and D<sup>a</sup> is the same as D<sup>b</sup> ("symmetrical" compounds).

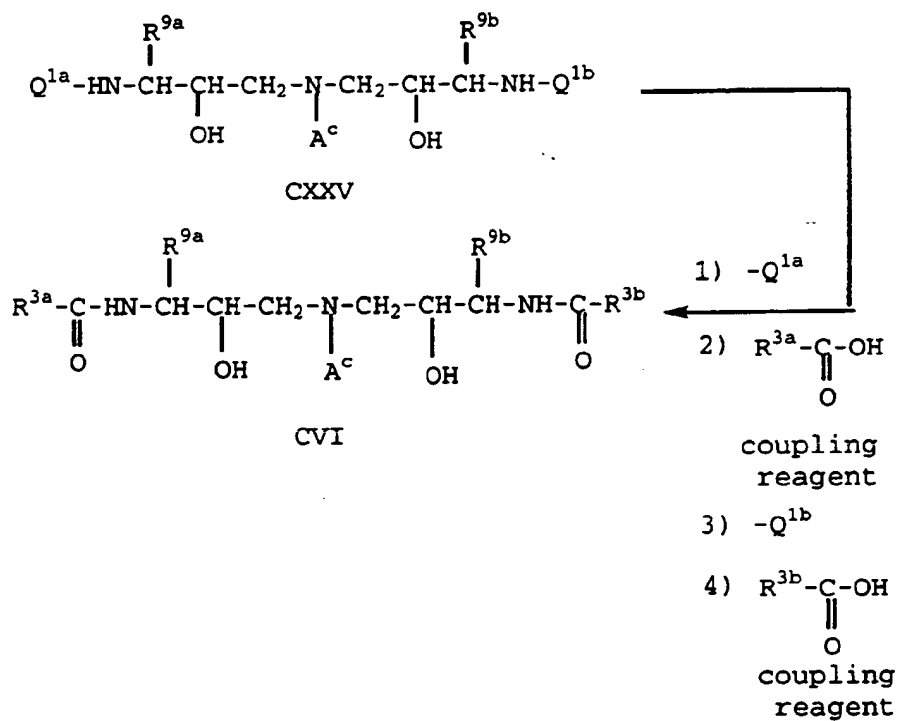
In Method (A), one equivalent of the bis-amine CXXIV (prepared as for XI where A<sup>c</sup> replaces Q<sup>3</sup>) is coupled to a carboxylic acid (prepared by standard techniques, where R<sup>3</sup> is described above and is compatible with the conditions used in the coupling reaction), using a coupling reagent such as DCC, EDCI, BOP reagent, BOP-Cl, DPPA, and the like, as described earlier (for alternative coupling conditions see Bodanszky, "Principles of Peptide Synthesis"; pp. 9-58, Springer-Verlag, (1984)) to give the aminediol CII. Where, in the bis-amine CXXIV, A<sup>c</sup> is hydrogen, the central amine to which it is bonded may optionally be protected as described above.

In Method (B), the process may be carried out in a step-wise fashion. The groups Q<sup>1a</sup> and Q<sup>1b</sup> in CXXV (prepared as for XXIII where A<sup>c</sup> replaces Q<sup>3</sup>) may be sequentially removed and the resulting amines coupled to a carboxylic acid to give the compound CII. Where A<sup>c</sup> is hydrogen, the central amine to which it is bonded may optionally be protected as described above.

Method (C) begins with removal of the group Q<sup>1a</sup> and coupling of the resulting amine with a carboxylic acid to give the azidoalcohol CIII. The azido moiety may be reduced and the resulting aminoalcohol CIV can be coupled to the epoxide XXI or the haloketone XXII, followed by reduction, to give the aminediol CV (see Reaction Scheme 3). The central amine may optionally be protected with A<sup>c</sup>. Removal of the group Q<sup>1b</sup> and coupling with a carboxylic acid as described above gives CII.

Reaction Scheme 11

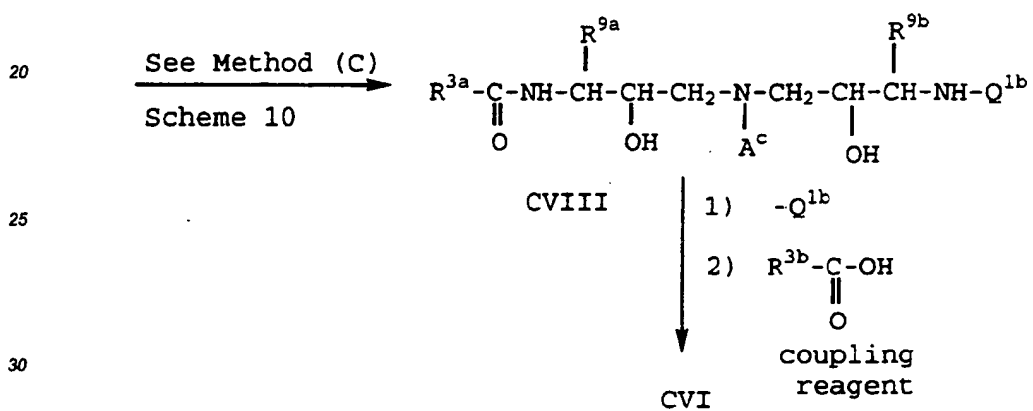
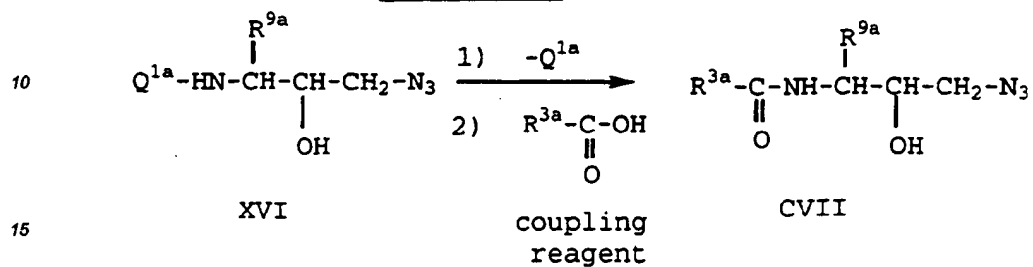
Alternative Methods for  
Preparation of Compounds I where  $A^a \neq A^b$   
and/or  $D^a \neq D^b$

Method (A)

## Reaction Scheme 11 (cont'd)

5

## Method (B)



35

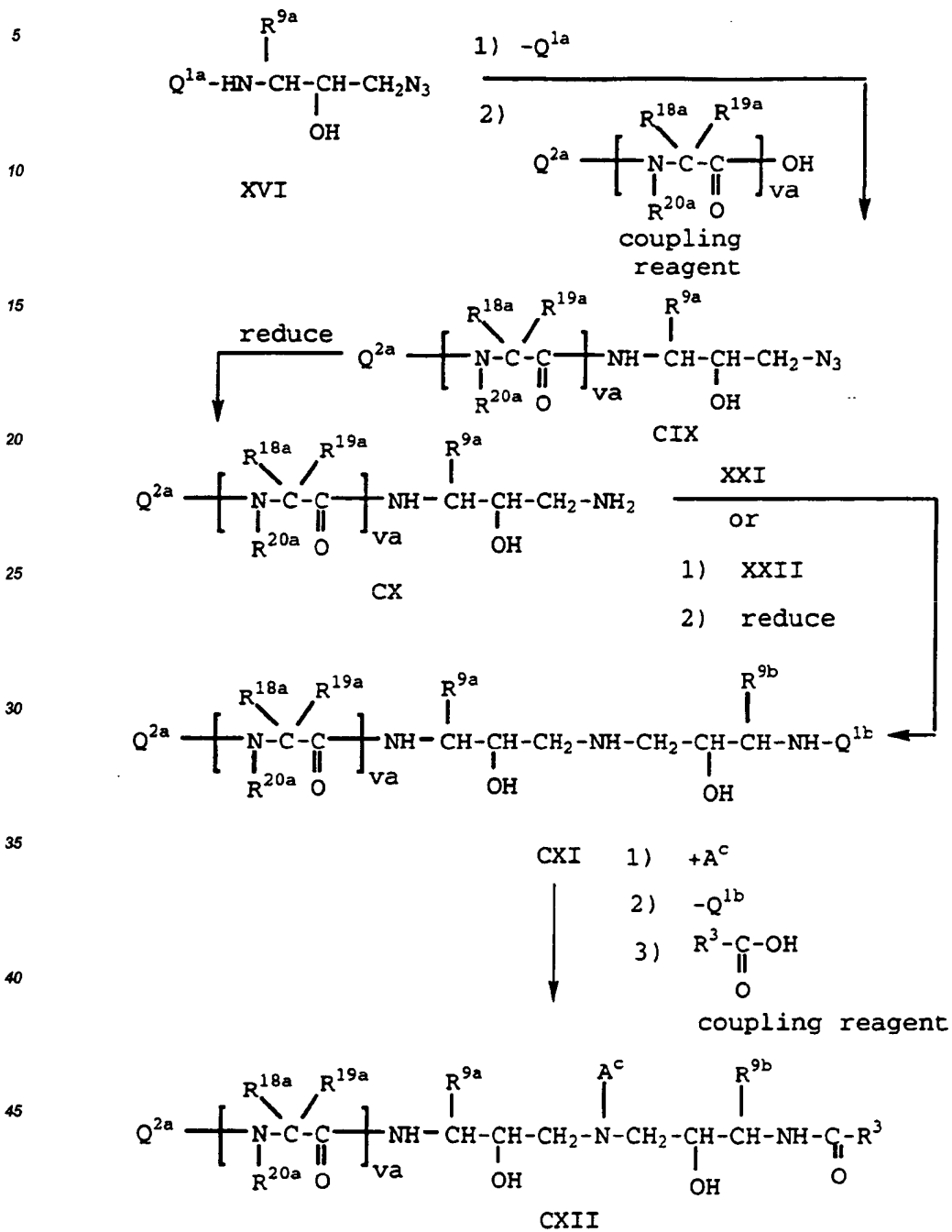
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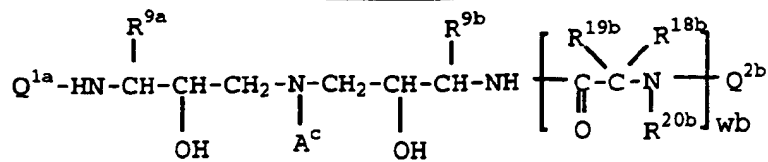
50

55

## Method (C)

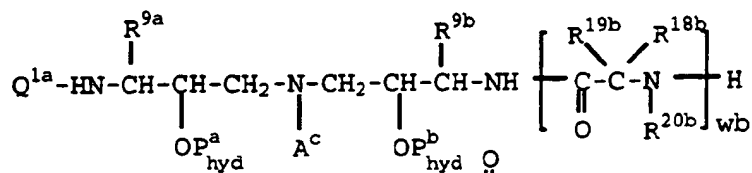


## Method (D)

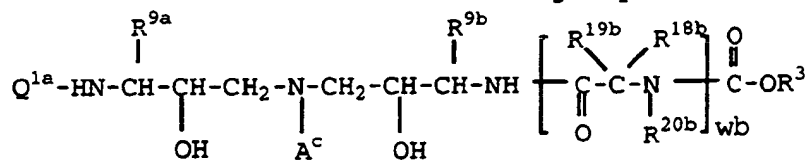


CXIII

1) Protect hydroxyl groups

2)  $-\text{Q}^{2b}$ 

CXIV

1)  $\text{Cl}-\text{C}(=\text{O})-\text{OR}^3$ 2)  $-\text{P}_{\text{hyd}}$  (deprotect hydroxyl groups)

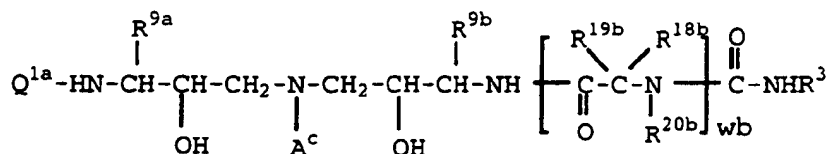
CXV



Method (E)

CXIV

- 1)  $R^3-N=C=O$  or  $R^3-NHCOC1$
- 2)  $-P_{hyd}$  (deprotect hydroxyl groups)

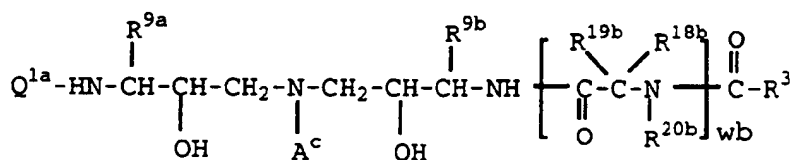


CXVI

Method (F)

CXIV

- 1)  $R^3-\overset{\overset{O}{||}}{C}-OH$   
coupling agent
- 2) deprotect hydroxyl groups



CXVII

Reaction Scheme 11 above illustrates Methods (A) through (F) which may be used to prepare compounds of the formula I where  $A^a$  differs from  $A^b$  and/or  $D^a$  differs from  $D^b$  ("non-symmetrical" compounds).

According to Methods (A) and (B), non-symmetrical compounds may be prepared by procedures analogous to those of Scheme 10. In Method (A), the groups  $Q^{1a}$  and  $Q^{1b}$  may be sequentially removed and the resulting amines coupled to carboxylic acids to give Compound CVI. Where  $A^c$  is hydrogen, the central amine to which it is bonded may optionally be protected as described above. Such compounds may also be prepared by employing Method (B), starting from azidoalcohol XVI and using procedures analogous to those of Method (C) of Reaction Scheme 10.

According to Method (C), non-symmetrical compounds may be prepared by procedures analogous to those of Reaction Schemes 2, 3 and 10. The method begins by removing the group  $Q^{1a}$  and coupling the resulting amine to N-protected amino acids or peptide chains to give the compound CIX. The azido moiety may be reduced and the resulting aminoalcohol CX can be coupled to the epoxide XXI, or to the haloketone XXII followed by reduction, as described in Methods (C) through (E) of Reaction Scheme 2, to give the aminodiol CXI. Optionally, the central amine may be protected and the  $Q^{1b}$  group may be removed and the resulting amine coupled to a suitable carboxylic acid by procedures analogous to those of Method (A) of Reaction Scheme 10 to give the aminodiol CXII.

Method (D) starts from compound CXIII (prepared as for XXIV where  $A^c$  replaces  $Q^3$  where  $w = 0-4$ ). The hydroxyl groups may optionally be protected such as with an ethoxyethyl group as described in Greene, Pro-

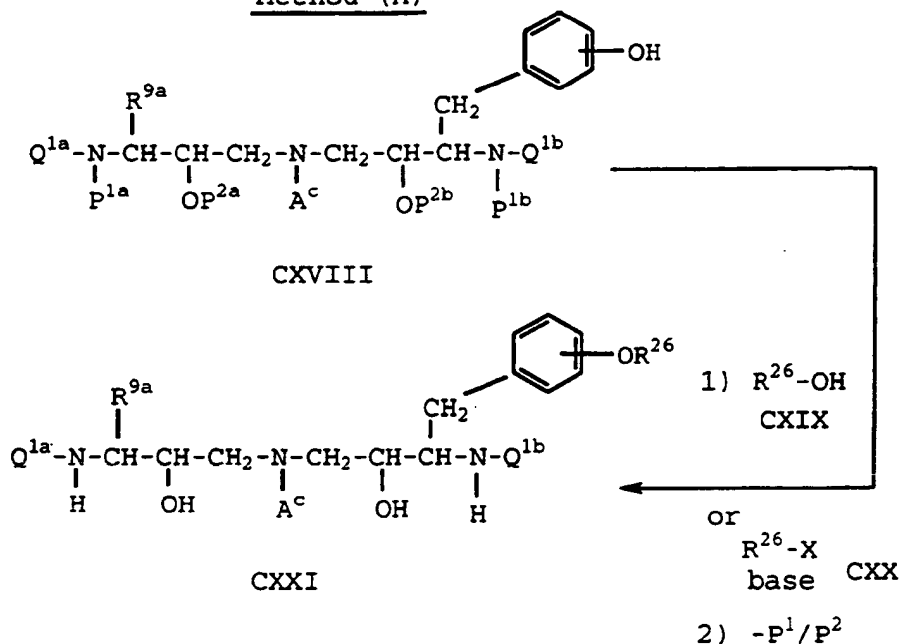
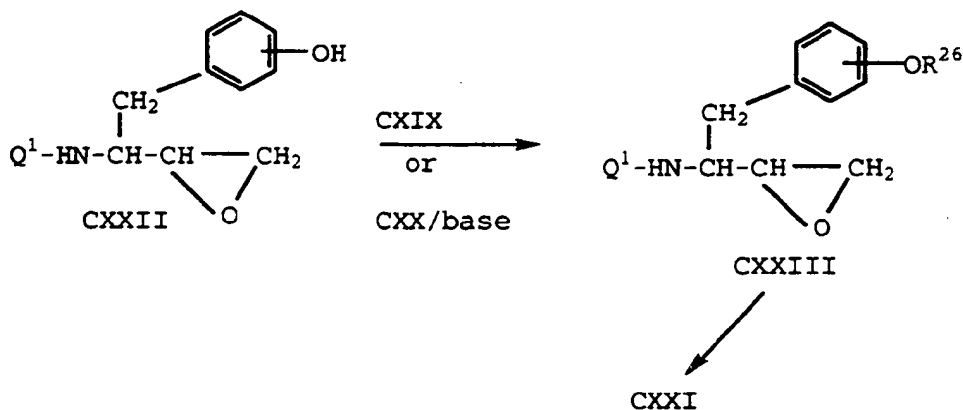
protective Groups in Organic Synthesis ( $P_{hyd}$  denotes a hydroxyl protecting group). The  $Q^{2b}$  group may then be removed and the resulting amine CXIV coupled with a chloroformate to afford, after removal of the hydroxyl protecting groups, the carbamate CXV. Where  $A^c$  is hydrogen, the central amine to which it is bonded may be protected as described above.

In Method (E), the amine CXIV may be coupled with an isocyanate compound or a carbamoyl chloride to provide, after removal of the hydroxyl protecting groups, the urea CXVI. Where  $A^c$  is hydrogen, the central amine to which it is bonded may be protected as described above.

In Method (F), the amine CXIV may be coupled with a carboxylic acid, using methods described in Scheme 10, to give, after removal of the hydroxyl protecting groups, the amide CXVII. Where  $A^c$  is hydrogen, the central amine to which it is bonded may optionally be protected as described above.

Reaction Scheme 12

Preparation of Compounds I where  $R^9$  = a  
Substituted (Hydroxyphenyl)methyl analog

Method (A)Method (B)

Reaction Scheme 12 above illustrates Methods (A) and (B) which may be used to prepare compounds of the formula I where  $R^9$  is a substituted (hydroxyphenyl)methyl group.

Compound CXVIII in which the nitrogens bear  $\text{P}^{1a}$  or  $\text{P}^{1b}$  ( $\text{P}^1$  denotes a nitrogen protecting group) and in which the hydroxyl groups are protected ( $\text{P}^2$  denotes a hydroxyl protecting group) of Method (A) may be prepared by methods described in Greene, Protective Groups in Organic Synthesis. In particular, the aforementioned nitrogen and hydroxyl oxygen may be connected by a one carbon linker to form an oxazolidine ring. The phenol may then be reacted with a suitable alcohol CXIX (where  $\text{R}^{26}$  is a lower alkyl group) in the presence of a phosphine (e.g., triphenylphosphine) and a reagent, such as diethyl- or diisopropylazodicarboxylate to give, after deprotection, the substituted phenol CXXI (Mitsunobu, Synthesis, 1 (1981); Varasi, et al., J. Org. Chem.,

52, 4235 (1987)).

Alternatively, phenol CXXVIII may be treated with a base, such as potassium carbonate, sodium or potassium hydride, sodium or potassium bis(trimethylsilyl)amide, or the like, and a suitably activated alkyl compound CXX where X can be a halogen, such as bromo, chloro, or iodo, or a sulfonate ester such as trifluoromethyl sulfonate (i.e.  $-O-SO_2-CF_3$ ) to give CXXI. Compound CXX can be prepared by methods known to those skilled in the art.

The aminediol CXXI may also be prepared as shown in Method (B). Procedures analogous to those of Method (A) above may be used to convert phenol CXXII (see Reaction Scheme 1 and Methods (A) and (B) of Reaction Scheme 9 for preparation) to epoxide CXXIII. Compound CXXIII may be converted to aminediol CXXI by procedures analogous to those of Methods (A), (B) and (E) of Reaction Scheme 2 and Methods (A) and (B) of Reaction Scheme 3.

Compounds of the formula I where  $R^{11}$  is not hydrogen may be obtained, for example, by methods known in the art for adding a hydroxyl protecting group, such as those described in Greene (referred to above).

Modifications to the processes of the above Reaction Schemes 1 to 12 may be made by one of ordinary skill in the art to obtain any of the compounds of the present invention. For example, protection and deprotection of groups may be suitably employed during such preparation.

### Preferred Compounds

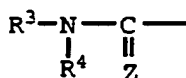
Preferred compounds of the formula I are those compounds containing the preferred groups described following.

$A^a$  and  $A^b$  are preferably, independently,

(A) hydrogen;

(B) alkyl such as unsubstituted lower alkyl or hydroxyalkyl;

(C) the group:

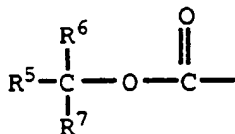


where Z is sulfur or, most preferably, oxygen;

$R^3$  is preferably alkyl such as unsubstituted lower alkyl (e.g., methyl or tert-butyl), arylalkyl (e.g., benzyl), or heterocycloalkyl (e.g., pyridylmethyl or benzimidazolymethyl); and

$R^4$  is preferably alkyl such as unsubstituted lower alkyl (e.g., methyl) or, most preferably,  $R^4$  is hydrogen;

(D) the group:

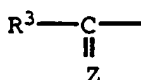


where

$R^5$  is

preferably hydrogen; carbocyclo (e.g., indenyl); alkyl such as unsubstituted lower alkyl (e.g., methyl, ethyl or tert-butyl) or alkyl which is substituted by one or more of amino, substituted amino (e.g., amino substituted by formyl, phenyl, benzyl or benzyloxycarbonyl), halo (e.g., fluoro), aryl (e.g., phenyl), hydroxy (e.g., mono or dihydroxy) or protected hydroxy, heterocyclo (e.g., dihydroindazolyl (optionally substituted by oxo and/or benzyl)), alkoxy (such as unsubstituted lower alkoxy (e.g., methoxy) or arylalkoxy (e.g., benzyloxy)), aryloxy (e.g., phenoxy), or arylaminocarbonyl (e.g., phenylaminocarbonyl); aryl (e.g., phenyl or biphenyl); heterocycl (e.g., imidazolyl (optionally substituted by trityl and/or phenyl), thiazolyl (optionally substituted by phenyl), 2-furo[2,3-c]pyridinyl, 2-furo[3,2-b]pyridinyl, 2-furo[2,3-b]pyridinyl, quinoxaliny, benzothiazolyl, quinolinyl, benzimidazolyl (optionally substituted by benzyloxyme-

- thyl), pyridyl, indolyl, oxazolidinyl (optionally substituted by oxo), dihydroisoin-  
dolyl (optionally substituted by oxo), 1,3-dioxolane (optionally substituted by  
methyl groups), dihydroquinazolinyl (optionally substituted by oxo), or benzox-  
azolyl); or alkynyl (e.g., phenylalkynyl); R<sup>5</sup> is most preferably hydrogen, alkyl  
(unsubstituted or substituted, in the latter case preferably hydroxyalkyl), aryl  
or heterocyclo;  
R<sup>6</sup> and R<sup>7</sup> are preferably hydrogen, or alkyl such as unsubstituted lower alkyl (e.g., me-  
thyl) or hydroxyalkyl; or  
two of R<sup>6</sup>, R<sup>6</sup> and R<sup>7</sup>, together with the carbon atom to which they are bonded, form a carbocyclo  
group (e.g., cyclobutyl or cyclopentyl (optionally substituted by hydroxy), or in-  
danyl (optionally further substituted by hydroxy or protected hydroxy)), or a het-  
erocyclo group (e.g., oxetanyl, tetrahydrofuryl (optionally substituted by hy-  
droxy), tetrahydro-1,1-dioxothienyl, tetrahydropyranyl, or benzimidazolyl (op-  
tionally substituted by methyl));  
(E) the group:



- where  
Z is sulfur or, most preferably, oxygen;  
R<sup>3</sup> is preferably hydrogen; aryl (e.g., phenyl or naphthyl); alkyl which is unsubstituted (e.g., ethyl or  
tert-butyl) or substituted by one or more of oxo, hydroxy (e.g., mono- or dihydroxy) or protected  
hydroxy, aryloxy (e.g., phenoxy or naphthyloxy), alkoxy (e.g., methoxy, benzyloxy, or benzimi-  
dazolylpropoxy), aryl (e.g., phenyl), heterocyclo (e.g., benzimidazolyl, 1,3-dioxolane (optionally  
substituted by methyl groups), indolyl, pyridyl, or dihydroindazolyl (optionally substituted by  
oxo)), oxime, alkoxyimino (e.g., methoxyimino), amino or substituted amino (e.g., benzyloxycar-  
bonylamino), alkylaminocarbonyl (e.g., N-methylaminocarbonyl), arylaminocarbonyl (e.g., phe-  
nylaminocarbonyl), alkylaminocarbonyloxy (e.g., N-methylaminocarbonyloxy), or fluoro (e.g., to  
form trifluoromethyl); carbocyclo (e.g., cyclopentyl or cyclohexyl (optionally substituted by me-  
thyl and/or hydroxy groups), or indanyl (optionally further substituted by hydroxy); or heterocyclo  
(e.g., quinoliny, pyrrolidinyl (optionally substituted by methyl and/or oxo groups), oxazolidinyl  
(optionally substituted by methyl and/or oxo groups), dihydroisoindolyl (optionally substituted by  
formyl), tetrahydrofuryl (optionally substituted by hydroxy and/or methyl groups), or benzimida-  
zolyl); R<sup>3</sup> is most preferably carbocyclo or alkyl wherein the carbocyclo or alkyl groups are sub-  
stituted, particularly by one or more of hydroxy, aryl, heterocyclo, alkylaminocarbonyl or fluoro  
(especially to form trifluoromethyl); or

(F) the groups:



or

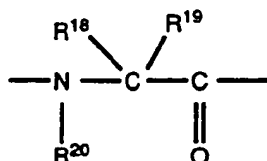


- where R<sup>3</sup> is alkyl, especially unsubstituted lower alkyl.

The above groups (C), (D) and (E) are most preferred as A<sup>a</sup> or A<sup>b</sup> substituents.

- A<sup>c</sup> is most preferably hydrogen. Where A<sup>c</sup> is other than hydrogen, preferred A<sup>c</sup> groups are alkyl-O-C(O)-,  
such as trialkylsilylalkyl-O-C(O)- (e.g., trimethylsilylethoxycarbonyl), fluorenylalkyl-O-C(O)- (e.g., fluorenylme-  
thoxycarbonyl) or arylalkyl-O-C(O)- (e.g., benzyloxycarbonyl); arylalkyl (e.g., benzyl); or unsubstituted lower  
alkyl (e.g., methyl).

E is preferably a single bond or a peptide chain containing 1 or 2 amino acids. Preferred amino acids are  
those wherein, in the formula:

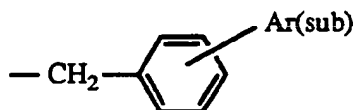


R<sup>18</sup> is hydrogen or unsubstituted lower alkyl (e.g., methyl);  
 R<sup>19</sup> is hydrogen, aryl (e.g., phenyl), or, most preferably, R<sup>19</sup> is lower alkyl which is unsubstituted (e.g., methyl, isopropyl, or tert-butyl) or which is substituted, particularly by one or more of hydroxy (or protected hydroxy), amino, aminocarbonyl, fluoro (e.g., to form trifluoromethyl), phenyl, or hydroxyphenyl; or  
 R<sup>18</sup> and R<sup>19</sup>, together with the carbon atom to which they are bonded, form a cycloalkyl group (e.g., cyclopentyl); and  
 R<sup>20</sup> is hydrogen or unsubstituted lower alkyl (e.g., methyl).  
 R<sup>1</sup> and R<sup>2</sup> are most preferably hydrogen. Where R<sup>1</sup> and R<sup>2</sup> are other than hydrogen, preferred R<sup>1</sup> and R<sup>2</sup> groups are arylalkyl (e.g., benzyl).

R<sup>8</sup> is preferably hydrogen; alkyl, especially unsubstituted lower alkyl (e.g., methyl); R<sup>8</sup> and R<sup>9</sup>, together with the atoms to which these groups are bonded, form a heterocyclo group (e.g., pyrrolidinyl or tetrahydroisoquinolinyl); R<sup>8</sup> and R<sup>11</sup>, together with the atoms to which these groups are bonded, form a heterocyclo group (e.g., 2,2-dimethyloxazolidinyl); or R<sup>8</sup> and A<sup>a</sup> or A<sup>b</sup> (as described above), together with the atoms to which these groups are bonded, form a heterocyclo group (e.g., 5,5-dimethyl-2-oxo-oxazolidinyl). R<sup>8</sup> is most preferably hydrogen.

R<sup>9</sup> is most preferably alkyl, especially unsubstituted lower alkyl (e.g., sec-butyl or isobutyl); or substituted lower alkyl, particularly:

- (A) cycloalkylalkyl (e.g., cyclohexylmethyl);
- (B) heterocycloalkyl, especially heterocyclomethyl (e.g., indolylmethyl, pyridylmethyl, or quinolinylmethyl);
- (C) arylalkenylalkyl, particularly where aryl is substituted by a group Ar(sub) defined below; or
- (D) arylalkyl, for example, phenylethyl, or, especially, a group of the formula:



where Ar(sub) is:

- (i) hydrogen;
- (ii) hydroxy;
- (iii) alkenyl (e.g., ethenyl);
- (iv) unsubstituted lower alkyl (e.g., ethyl); or
- (v) alkoxy, especially:
  - unsubstituted lower alkoxy (e.g., methoxy);
  - alkoxyalkoxy (e.g., methoxyethoxy, methoxybutoxy, benzyloxyethoxy, or benzyloxypropoxy);
  - hydroxyalkoxy (e.g., hydroxyethoxy, hydroxypropoxy, or hydroxybutoxy);
  - arylalkoxy (e.g., benzyloxy);
  - heterocycloalkoxy (e.g., morpholinylpropoxy, morpholinylethoxy, 3-oxo-morpholinylethoxy, pyridylethoxy, benzoxazolylmethoxy, benzoxazolylpropoxy, imidazolylethoxy, 2-oxo-oxazolidinylethoxy, 3-methyl-2-oxo-imidazolidinylethoxy, 2-hydroxy-2-pyridylethoxy);
  - aminoalkoxy (e.g., aminoethoxy) or aminocarbonyloxyalkoxy (e.g., aminocarbonyloxyethoxy), especially where the amino moiety is unsubstituted or mono- or disubstituted by alkyl (e.g., methyl) or aryl (e.g., tolyl);
  - heterocyclocarbonylalkoxy (e.g., morpholinylcarbonylethoxy, morpholinylcarbonylmethoxy or piperidinylcarbonylmethoxy);
  - heterocyclooxyalkoxy (e.g., pyridyloxyethoxy);
  - alkoxycarbonylalkoxy (e.g., ethoxycarbonylmethoxy); or
  - carboxyalkoxy (e.g., carboxymethoxy).

Where R<sup>9</sup> is other than alkyl, preferred R<sup>9</sup> groups are hydrogen; aryl; alkenyl; carbocyclo; or R<sup>9</sup> and R<sup>8</sup>, together with the atoms to which these groups are bonded, form a heterocyclo group (e.g., pyrrolidinyl or tetrahydroisoquinolinyl).

R<sup>9</sup> is preferably hydrogen.

R<sup>10</sup> is most preferably hydrogen. Where R<sup>10</sup> is other than hydrogen, preferred R<sup>10</sup> groups are arylalkyl (e.g., benzyl); unsubstituted lower alkyl (e.g., methyl); or R<sup>10</sup> and R<sup>11</sup> together form a keto group.

R<sup>11</sup> is most preferably hydrogen. Where R<sup>11</sup> is other than hydrogen, preferred R<sup>11</sup> groups are alkoxyalkyl (e.g., ethoxyethyl); unsubstituted lower alkyl (e.g., methyl); R<sup>11</sup> and R<sup>8</sup>, together with the atoms to which these

groups are bonded, form a heterocyclic group (e.g., 2,2-dimethyl azolidinyl); or R<sup>11</sup> and R<sup>10</sup> together form a keto group.

p and q are preferably 0.

5 Particularly preferred compounds of the present invention are the following compounds, and salts and/or stereoisomers thereof, prepared as the title compounds of the following Examples of this specification: 2, 21, 76, 93, 104, 162, 175, 178, 209, 224, 226, 234, 246, 257, 262, 271, 282, 293, 297, 298, 304, 308, 311, 322, 327, 331, 333, 334, 336, 339, 344, 352, 355, 356, 359, 366, 368, 377 and 383.

#### 10 Preferred Utility

Proteases are enzymes which cleave proteins at specific peptide bonds and, in living systems, mediate or control a broad spectrum of biological functions, such as cleaving precursors to form active proteins in post-translational processing of polypeptides. For example, retroviral proteases cleave large precursor polypeptides, produced in infected cells, into smaller protein components, or subunits, which are subsequently assembled to form functional virus structures. As proteases encoded by the viral genome play a critical role in the replication of a virus, these enzymes represent targets for therapeutic agents.

Retroviruses are viruses which contain two copies of their RNA genome, each of which is copied into a double strand of DNA using a retroviral enzyme reverse transcriptase (RT). A second retroviral enzyme, ribonuclease H, is part of the RT protein and facilitates the synthesis of the DNA:DNA duplex. A third retroviral enzyme called integrase splices the double stranded DNA copy of the virus into the chromosome of the host cell. A fourth retroviral enzyme cell protease is critical to the process of viral replication by cleaving polypeptide precursors into required enzymes and structural proteins.

The compounds of the present invention inhibit retroviral proteases, thereby inhibiting viral replication, and are thus especially useful in the treatment and/or prevention of retroviral infections caused by such pathogenic organisms.

Exemplary protease-encoding retroviruses, the replication of which may be inhibited by the compounds of the present invention include the human T-cell lymphotropic viruses, HTLV-I and HTLV-II, the human immunodeficiency viruses, for example, HIV-1, HIV-2 or mutants thereof (AIDS pathogens), feline leukemia virus and simian immunodeficiency virus. Protease inhibition may be assayed by methods such as those described below in the Examples section of the present specification. The compounds of the present invention may, of course, be used to simultaneously inhibit the replication of two or more retroviruses, as well as to inhibit the replication of a single retrovirus.

The compounds of the present invention are particularly useful in the inhibition of human immunodeficiency virus (HIV) protease, and thus in the prevention and/or treatment of infection by HIV viruses (HIV-1, HIV-2, and mutants thereof), including the treatment of consequent pathological conditions such as AIDS.

HIV protease is a retroviral protease which processes the gag polyprotein precursor into core proteins and the pol polyprotein precursor into reverse transcriptase, integrase, and the protease itself. HIV protease is essential for the correct processing of these polyproteins and the production of infectious viral particles, as evidenced by the fact that mutations of the protease gene result in non-infectious viral particles with an immature morphology. Inhibition of HIV protease is thus a highly attractive target for anti-HIV therapy.

Use of the compounds of the present invention in inhibiting HIV protease includes, but is not limited to, treating a wide range of states of HIV infection such as treating or preventing AIDS or ARC (AIDS related complex), treating both symptomatic and asymptomatic HIV-infected patients, and treating actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, accidental needle stick, or exposure to patient blood during surgery.

As indicated above, the compounds of the present invention may also be useful in the treatment and/or prevention of infections caused by other retroviruses. Exemplary retroviruses that are pathogenic in man in addition to the human immunodeficiency viruses are HTLV-1 and HTLV-2. Exemplary viruses pathogenic in other species are feline leukemia virus and simian immunodeficiency virus.

The present invention also provides pharmaceutical compositions comprising at least one of the inventive compounds capable of inhibiting retroviral protease in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds may, for example, be administered orally, such as in the form of tablets, capsules, granules or powders; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g. as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; or rectally such as in the form of suppositories;

in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compositions may, for example, be administered liposomally.

When administered orally, the compositions may be prepared according to techniques well known in the art of pharmaceutical formulation. As a suspension they may, for example, contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents known in the art. As immediate release tablets, the present compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, the compositions may be prepared according to techniques well known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents known in the art.

When administered as injectable solutions or suspensions, the present compositions may be formulated according to techniques well known in the pharmaceutical art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by techniques well known in the pharmaceutical art by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

The pharmaceutical compositions of the present invention may contain an amount of the inventive compound(s) effective for the inhibition of retroviral replication, and preferably an amount effective for the treatment and/or prevention of infection by HIV. The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes amounts such as those from about 1 to 150 mg/kg of body weight of active compound per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

Viral hosts which are preferred subjects for treatment and/or prevention of retroviral infections include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like. A dose for adult humans is preferably between about 10 and about 50 mg/kg of body weight per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 - 4 times per day.

The compounds of the present invention may be employed alone or in combination with other suitable therapeutic agents useful in the treatment of retroviral infections such as AIDS, such as other antiviral agents, immunomodulators, antibiotics or vaccines.

Other therapeutic agents may include, but are not restricted to the following: antivirals exemplified by AL-721, interferon beta, polymannoacetate, ganciclovir, DDC (dideoxycytidine), d4T, DDI (dideoxyinosine), Foscarnet (trisodium phosphonoformate), HPA-23, efloornithine, Peptide T (octapeptide sequence), Reticulose (nucleophosphoprotein), AZT, ansamycin LM 427, trimetrexate, UA-001, ribavirin,  $\alpha$ -interferon, acyclovir, 3TC, PMEA, nevirapine, pyridinones (e.g. L-697,661), BHAPs (e.g. U-90152), alpha-APA derivatives (e.g. R 18893), TIBO derivatives (e.g. R 82913), and Ro 31-8959; immunomodulators exemplified by bropirimine, Ampligen (mismatched RNA), Anti-human alpha interferon antibody, Colony Stimulating Factor (GM-CSF), CL246,738, IMREG-1, IMREG-2, diethyl dithio carbamate, interleukin-2, inosine pranobex, methionine enkephalin, MTP-PE (muramyl-tripeptide), Thymypentin (TP-5) (thymic compound), recombinant erythropoietin, naltrexone, TNF (tumor necrosis factor); and antibiotics exemplified by Pentam 300 (pentamidine isethionate).

In particular, the HIV protease inhibitors of the present invention may be used in combination with other anti-retroviral therapies for the treatment of AIDS. Such combined therapies may include, but are not limited to, a compound of the present invention in combination with: other (e.g., those other than inhibitors of the present invention) HIV protease inhibitors (e.g. Ro 31-8959); nucleoside and non-nucleoside reverse transcriptase inhibitor(s), preferably nucleoside reverse transcriptase inhibitors such as AZT, DDI, d4T, DDC, 3TC or PMEA, and non-nucleoside reverse transcriptase inhibitors such as nevirapine, pyridinones (e.g. L-697,661), BHAPs (e.g. U-90152), alpha-APA derivatives (e.g., R 18893), and TIBO derivatives (e.g. R 82913); inhibitor(s) of *tat* such as RO24-7429; drug(s) which inhibit binding of the virus to CD<sub>4</sub> receptors; inhibitor(s) of RNAs polymerase, *int* gene, or *rev*; and immunomodulator(s) such as IFN- $\alpha$  ( $\alpha$ -interferon).

The above compounds to be employed in combination with the compounds of the present invention will



used, for example, in amounts as indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. The aforementioned combined therapies may, for example, be conducted simultaneously or sequentially.

5 The instant invention also provides methods for the inhibition of retroviral proteases by contacting said protease with a compound of the present invention capable of said inhibition, and particularly for the treatment and/or prevention of retroviral infections. Treatment and/or prevention of infection by the human immunodeficiency viruses is preferred. The methods of the present invention preferably comprise the step of administering to a subject in need thereof one or more of the present compounds capable of treatment and/or prevention of  
10 retroviral infection in an amount effective therefor. Other therapeutic agents such as those described above may be employed with the inventive compounds in the present methods.

The compounds of the present invention are also useful in the preparation of other compounds of the formula I. Thus, for example, one compound of the present invention may be employed in the preparation of another compound of the present invention, where the latter compound has greater potency against the same  
15 or a different retrovirus than the former.

The following Examples will serve to illustrate the preparation of compounds of the present invention, and are not intended to limit the scope or spirit of the instant claims. The following abbreviations are employed in the Examples:

## 20 Abbreviations

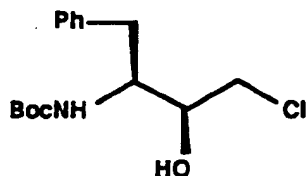
Ph = phenyl  
Bn = benzyl  
t-Bu = tertiary-butyl  
25 Me = methyl  
Et = ethyl  
Ts = tosyl (p-toluenesulfonyl)  
Bz = benzoyl  
Phe = phenylalanine  
30 Val = valine  
TMS = trimethylsilyl  
TBS or TBDMS = tert-butyldimethylsilyl  
Fmoc = fluorenylmethoxycarbonyl  
Teoc = trimethylsilyloxyethoxycarbonyl  
35 Boc = tert-butoxycarbonyl  
Cbz or Z = carbobenzyloxy (or carbobenzyloxy or benzyloxycarbonyl)  
THF = tetrahydrofuran  
Et<sub>2</sub>O = diethylether  
EtOAc = ethyl acetate  
40 DMF = dimethylformamide  
MeOH = methanol  
EtOH = ethanol  
i-PrOH = iso-propanol  
t-BuOH = tert-butanol  
45 DMSO = dimethylsulfoxide  
DME = 1,2-dimethoxyethane  
HMPA = hexamethylphosphoric triamide  
HOAc or AcOH = acetic acid  
TFA = trifluoroacetic acid  
50 i-Pr<sub>2</sub>NEt = diisopropylethylamine  
Et<sub>3</sub>N = triethylamine  
DMAP = 4-dimethylaminopyridine  
MeLi = methyl lithium  
n-BuLi = n-butyllithium  
55 s-BuLi = sec-butyllithium  
n-Bu<sub>4</sub>NF·nH<sub>2</sub>O = tetra-n-butylammonium fluoride hydrate  
n-Bu<sub>4</sub>NBr = tetra-n-butylammonium bromide  
n-Bu<sub>4</sub>NI = tetra-n-butylammonium iodide  
EDC (or EDC-HCl) or EDCI (or EDCI-HCl) = 3-ethyl-3'-(dimethylamino)propylcarbodiimide hydrochloride (or

- 1-(3-dimethylamin propyl)-3-ethylcarbodiimid hydrochloride)  
 HOBT or HOBT·H<sub>2</sub>O = 1-hydroxybenzotriazol hydrate  
 KN(TMS)<sub>2</sub> = potassium bis(trimethylsilyl)amide NaN(TMS)<sub>2</sub> = sodium bis(trimethylsilyl)amid  
 5 Boc-ON = [2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile]  
 AcCl = acetyl chloride  
 BOP-Cl = Bis(2-oxo-3-oxazolidinyl)phosphinic chloride  
 BOP reagent = benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate  
 PPh<sub>3</sub> = triphenylphosphine  
 10 DEAD = diethylazodicarboxylate  
 Me<sub>2</sub>S = dimethylsulfide  
 Ti(*i*-Pro)<sub>4</sub> = titanium(IV) isopropoxide  
 KOAc = potassium acetate  
 Dibal or DIBAL-H = diisobutylaluminum hydride  
 15 Cbz-Cl = carbobenzoxy chloride (benzyl chloroformate)  
 PMA = phosphomolybdic acid  
 min = minute(s)  
 h or hr = hour(s)  
 L = liter  
 20 ml or mL = milliliter  
 µl or µL = microliter  
 g = gram(s)  
 mg = milligram(s)  
 mol = mole(s)  
 25 mmol = millimole(s)  
 RT = room temperature  
 sat. or sat'd. = saturated  
 aq. = aqueous  
 TLC = thin layer chromatography  
 30 HPLC = high performance liquid chromatography  
 UV = ultraviolet  
 MS or Mass Spec. = mass spectrometry  
 NMR = nuclear magnetic resonance  
 mp = melting point  
 35 hex = hexane  
 Tf = triflate  
 NaHB(OAc)<sub>3</sub> = sodium triacetoxyborohydride  
 p-TsOH = p-toluenesulfonic acid  
 m-CPBA = metachloroperbenzoic acid  
 40 DCC = dicyclohexylcarbodiimide  
 NBS = N-bromosuccinimide  
 PPTs = Pyridinium p-tosylate  
 PCC = pyridinium chlorochromate  
 BF<sub>3</sub>·Et<sub>2</sub>O = boron trifluoride etherate  
 45 Compounds in the following Examples are referred to by the step and number of the Example in which they are prepared. For example, "Compound 1c" denotes the compound prepared in step (c) of Example 1; "Compound 39" denotes the compound prepared in Example 39, which Example contains a single step.

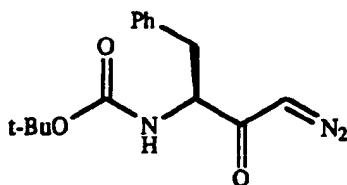
#### Example 1

- 50 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1, 1-dimethylethyl ester (Compound 1c)

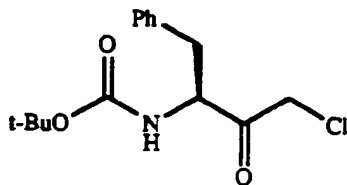
55

(a) Compound 1a(iv)(i) Diazomethane-Et<sub>2</sub>O solution

To the mixture of 40% aqueous KOH (75 ml) and Et<sub>2</sub>O (255 ml) cooled at 0°C was added 1-methyl-3-nitro-1-nitrosoguanidine (23.85 g, 162.2 mmol) portionwise. The mixture was swirled several times during each addition. After 10 min, the resulting yellow Et<sub>2</sub>O layer was decanted over KOH pellets at 0°C and dried for 2.0 h at 0°C.

(ii) Compound 1a(ii)

To the solution of N-Boc-L-phenylalanine (14.34 g, 54.05 mmol) in dry THF (80 ml) cooled at -20°C to -25°C (dry ice-CCl<sub>4</sub> bath) was added isobutyl chloroformate (7.01 ml, 54.05 mmol) over 5 min, followed by 4-methylmorpholine (5.94 ml, 54.05 mmol) and the mixture was stirred for 20 min. The white precipitate was removed by filtration under argon atmosphere and washed with ca. 70 ml of dry THF. The combined THF solution of mixed anhydride was cooled to -5°C and poured into the above prepared diazomethane in Et<sub>2</sub>O solution at 0°C. The resulting yellow solution was kept at 0°C for 2.0 h, then RT overnight. N<sub>2</sub> was then bubbled through the light-yellow solution for 30 min, and Et<sub>2</sub>O (400 ml) then added. The solution was washed with H<sub>2</sub>O (400 ml), saturated NaHCO<sub>3</sub> (300 ml) and brine (300 ml), and was dried over anhydrous MgSO<sub>4</sub>. Concentration *in vacuo* afforded a yellow residue, which was triturated with hexane to give, after drying over P<sub>2</sub>O<sub>5</sub> overnight under high vacuum, 14.72 g (94%) of the title α-diazoketone as a pale yellow solid. This material was used immediately in the reaction of the next step without further purification.

(iii) Compound 1a(iii)

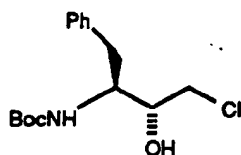
To the solution of the crude α-diazoketone prepared above (14.72 g, 50.87 mmol) in dry Et<sub>2</sub>O (500 ml) cooled at 0°C was added, dropwise, a solution of 4N HCl in dioxane (12.72 ml, 50.87 mmol) while maintaining the temperature below 5°C. The reaction mixture was then stirred at 0°C for 1.0 h. TLC (hexane-EtOAc 4:1) showed trace amounts of the starting α-diazoketone remained. Additional 4N HCl in dioxane (636 μl, 0.05 eq., 2.54 mmol) was added and the mixture was stirred at 0°C for one additional hour.

Concentration *in vacuo* gave a residue which was dissolved in hot Et<sub>2</sub>O (60 ml). Hexane (200 ml) was slowly added and the mixture allowed to stand for 2.0 h at 5°C. The solid was filtered and dried *in vacuo* over P<sub>2</sub>O<sub>5</sub> under high vacuum to afford 9.58 g (first crop) of the title α-chloroketone. The filtrate was concentrated to dryness and the residue was again recrystallized from Et<sub>2</sub>O-hexane to give an additional 4.41 g (second crop) of the above

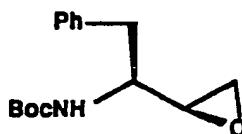
$\alpha$ -chloroketone. Total yield: 13.99 g (92%).

(iv) Compound 1a(iv)

NaBH<sub>4</sub> (1.59 g; 42 mmol) was added to a solution of the  $\alpha$ -chloroketone prepared above (5 g; 16.8 mmol) in 84 ml of THF and 9 ml of H<sub>2</sub>O at 0°C. After stirring at 0°C for 45 min the reaction mixture was concentrated to dryness. The residue was stirred at 0°C with EtOAc (150 ml) and H<sub>2</sub>O (25 ml) while saturated KHSO<sub>3</sub> solution was carefully added until the pH was ~1.5. This mixture was then diluted with 350 ml of EtOAc and the layers were separated. The organic layer was washed with H<sub>2</sub>O (100 ml) and brine (100 ml). After drying over MgSO<sub>4</sub>, the organic layer was concentrated to a white solid. A portion of this solid (4.89 g) was recrystallized from 70 ml of hot EtOAc to afford 2.47 g (50%) of Compound 1a(iv) as a white solid containing a few percent of its diastereomer, the following Compound 1a(v):

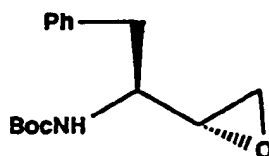


(b) Compound 1b(i)



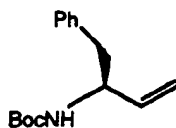
0.71M KOH in EtOH (14.7 ml; 10.4 mmol) was added to a suspension of Compound 1a(iv) (2.6 g; 8.67 mmol) in 87 ml of EtOH at RT. The reaction was stirred 1.5 h at RT, during which time the thick suspension became a fine powdery one. At this time, the EtOH was removed *in vacuo* and the residue was partitioned between EtOAc (200 ml) and H<sub>2</sub>O (200 ml). The organic layer was washed with saturated NH<sub>4</sub>Cl solution (2 x 100 ml), H<sub>2</sub>O (2 x 100 ml), and brine (100 ml). After drying over MgSO<sub>4</sub>, the EtOAc was removed *in vacuo* and the solid white residue was recrystallized by dissolving in 10 ml of refluxing EtOAc and adding 190 ml of hexane. The resulting crystalline suspension was allowed to cool to -40°C and stand overnight. Filtration, rinsing with hexane, and drying under high vacuum for two hours afforded 1.92 g (84%) of Compound 1b(i) as a colorless crystalline solid. This material was 99.1% diastereomerically pure by HPLC.

Compound 1b(ii)



The diastereomeric epoxide 1b(ii) is prepared by a procedure analogous to the one used for 1b(i) starting from the minor diastereomeric chlorohydrin isolated by column chromatography from 1a(iv) above.

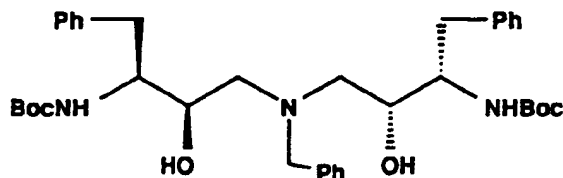
Alternatively, to a solution of the compound:



(for preparation, see Luly et al., *J. Org. Chem.*, 52, 1487 - 1492 (1987)) in dioxane at 0°C was added a sus-

p nsion of NBS in H<sub>2</sub>O. After 5 min, the reaction mixture was warmed to RT and stirred for 2.0 h. Th r action mixture was then diluted with MeOH and K<sub>2</sub>CO<sub>3</sub> was added. Aft r 3.0 h, the volatiles were removed *in vacuo* and th residue was partition d betw n CH<sub>2</sub>Cl<sub>2</sub> and H<sub>2</sub>O. Th organic lay r was conc ntrat d *in vacuo* to giv a mixture f Compounds 1b(i) and 1b(ii) (3:1 mixture, 1b(i): 1b(ii)) as a colorless solid.

(c) Compound 1c



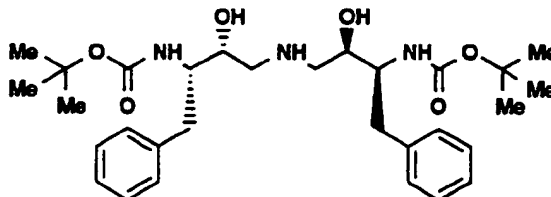
A DMF (2.5 mL) solution of Compound 1b(i) (1.97 g, 7.48 mmol) and benzyl amine (0.41 mL, 3.74 mmol) was heated under argon for 7 h at 105 - 108°C, then stirred overnight at RT. After heating an additional 1.5 h at 105 - 108°C, the volatiles were evaporated *in vacuo*. The resulting residue was co-evaporated twice with MeOH/CH<sub>2</sub>Cl<sub>2</sub> and purified by flash column chromatography (silica gel, 5 by 19 cm), eluting with 0.5, 1, 2, 3, 4, 7, and then 10% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to give Compound 1c (1.39 g, 56% yield) as a colorless solid.

Anal. Calc. for C<sub>37</sub>H<sub>51</sub>N<sub>3</sub>O<sub>5</sub> · 1.63 H<sub>2</sub>O:

	C, 68.68;	H, 8.45;	N, 6.49
Found:	C, 68.35;	H, 8.10;	N, 6.82

Example 2

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 2)



To an EtOH (5 mL) solution of Compound 1c (90 mg, 0.142 mmol) and cyclohexene (2.5 mL) at RT was added Pd(OH)<sub>2</sub> (41 mg, 20% on carbon). The reaction mixture was refluxed at 90°C for 1 h, filtered hot through Celite, and the volatiles were removed *in vacuo* to leave a colorless solid (74 mg). The residue was purified by flash chromatography (silica gel, 1 by 12.5 cm), eluting with 0.5, 2, 4, 8, and then 9% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to give the title Compound 2 (53 mg, 69% yield) as a colorless solid. m.p. 178-179.5°C; [α]<sub>D</sub> = -7.07° (c 0.1, MeOH). MS: 544 (M+H).

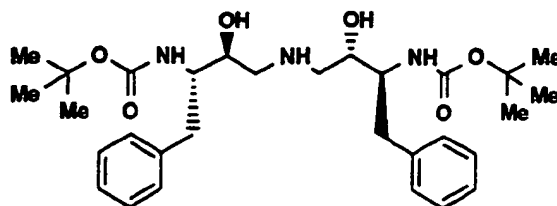
Anal. Calc. for C<sub>30</sub>H<sub>45</sub>N<sub>3</sub>O<sub>8</sub> · 0.8 H<sub>2</sub>O:

	C, 64.57;	H, 8.42;	N, 7.53
Found:	C, 64.53;	H, 8.30;	N, 7.57

Exmpl 3

Preparation of [1S-[1R\*,2R\*(2R\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 3)

tyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 3)



Compound 1b(ii) was converted to the title Compound 3 by procedures analogous to those described for Compounds 1c and 2.

m.p. 140-141°C;  $[\alpha]_D^{25} = -42.38^\circ$  (c 0.29, MeOH).

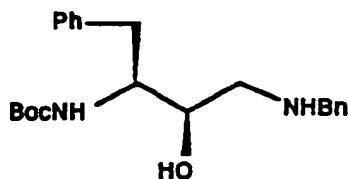
MS: 544 (M+H).

Anal. Calc. for $C_{30}H_{46}N_2O_8 \cdot 1.45 H_2O$ :			
	C, 63.24;	H, 8.47;	N, 7.37
Found:	C, 63.25;	H, 8.36;	N, 7.36

#### Example 4

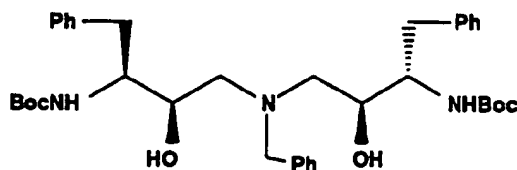
Preparation of [1S-[1R\*,2S\*(2R\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 4b)

##### (a) Compound 4a



A DMF (0.4 mL) solution of Compound 1b(i) (75 mg, 0.285 mmol) and benzyl amine (0.025 mL, 0.229 mmol) was heated for 18 h at 85°C and the volatiles were evaporated *in vacuo* at 30°C. The solid residue (100 mg) was purified by flash column chromatography (silica gel, 1.5 by 11 cm), eluting with 0.5, 4, and then 8% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to give Compound 4a (50 mg, 41% yield) as a colorless solid.

##### (b) Compound 4b

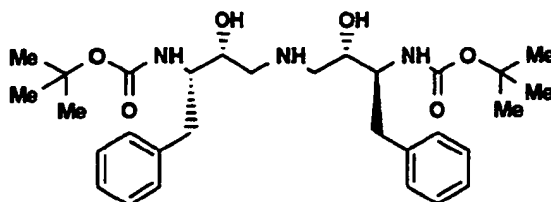


A DMF (0.3 mL) solution of Compound 4a (48 mg, 0.11 mmol) and Compound 1b(ii) (55 mg, 0.21 mmol) was heated for 7 h at 105-110°C, then stored at -40°C overnight. After warming to RT, the volatiles were evapo-

rated *in vacuo* at 30°C. The oily-solid residu (120 mg) was purified by flash column chromatography (silica gel, 1 by 16 cm), eluting with 0.5, 1, 1.5, and then 2% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to give Compound 4b (74 mg, ~100% yield) as a colorless solid. *R<sub>f</sub>* = 0.69 (7% MeOH:CH<sub>2</sub>Cl<sub>2</sub>).

### Example 5

Preparation of [1S-[1R\*,2S\*(2R\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 5)



Compound 4b was deprotected using a procedure analogous to that for Compound 2 to give the title Compound 5.

m.p. 151-153°C; [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -22.93° (c 0.23, MeOH).

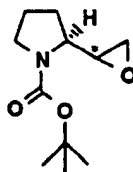
MS: 544 (M+H).

Anal. Calc. for C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>8</sub> · 0.67 H <sub>2</sub> O:			
	C, 64.83;	H, 8.40;	N, 7.56
Found:	C, 64.84;	H, 8.37;	N, 7.55

### Example 6

Preparation of (2S)-2,2'-[(Phenylmethyl)iminobis[1-hydroxy-2,1-ethanediyl]bis-1-pyrrolidine-carboxylic acid], bis(1,1-dimethylether)ester, single isomer (A) (Compound 6b)

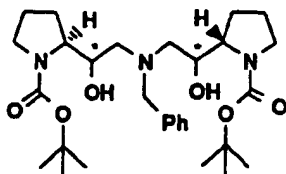
(a) Compounds 6a(i) and 6a(ii)



Compound 6a(i) faster moving isomer

Compound 6a(ii) slower moving isomer

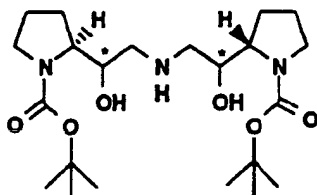
Compounds 6a(i) and 6a(ii) (unknown stereochemistry) were prepared by a procedure analogous to the synthesis of Compounds 1b(i) and 1b(ii) in which Boc-(L)-proline was employed in place of N-Boc-L-phenylalanine.

(b) Compound 6b

Compound 6a(ii) was converted to the title Compound 6b by opening with benzyl amine and then reacting with another molecule of 6a(ii) analogous to the two-step procedure used for the preparation of Compound 4b.  $R_f = 0.36$  (3:1 EtOAc/hexane) (oil).

Example 7

Preparation of (2S)-2,2'-[Iminobis(1-hydroxy-2,1-ethanediy)]bis-(1-pyrrolidinecarboxylic acid), bis(1,1-dimethylethylether)ester, single isomer (A) (Compound 7)



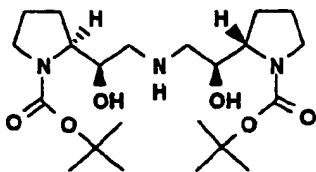
A suspension of 0.069 g (0.13 mmol) of Compound 6b and 10 mg of  $\text{Pd}(\text{OH})_2$  in 1.5 ml of MeOH was stirred under a  $\text{H}_2$  atmosphere (balloon) at RT overnight. The mixture was filtered through a micropore fritted funnel (MeOH wash) and evaporated. The crude product was purified by flash chromatography (20mm X 6"; 10% MeOH/ $\text{CH}_2\text{Cl}_2$  + 1%  $\text{NH}_4\text{OH}$ ) to give 41 mg (<72%) of slightly impure material. This material was combined with 41 mg of material from a previous reaction and recrystallized from EtOAc/Hexane to give 32 mg of the title Compound 7 as a white solid.  
m.p. = 181-184°C;  $[\alpha]_D^{25} = -86^\circ$  (c 0.1, MeOH). MS: 444 (M+H).

Anal. Calc. for  $\text{C}_{22}\text{H}_{41}\text{N}_3\text{O}_8 \cdot 0.52 \text{ H}_2\text{O}$ :

	C, 58.34;	H, 9.35;	N, 9.28;
Found:	C, 58.39;	H, 9.44;	N, 9.23.

Example 8

Preparation of [S-(R\*,R\*)]-2-[2-[[[S-(R\*,S\*)]-2-[1-[(1,1-Dimethylethoxy)carbonyl]-pyrrolidinyl]-2-hydroxyethyl]amino]-hydroxyethyl]-1-pyrrolidine-carboxylic acid, (1,1-dimethylethyl) ester (Compound 8)



Compounds 6a(i) and 6a(ii) were converted to the title Compound 8 (white solid) by procedures analogous to those used for the synthesis of Compound 7 except that epoxide 6a(ii) was opened with 2 equivalents of



b nzy l amine and th resulting product was reacted with epoxid 6a(i) by a procedure analogous to that used for Compound 4b.

m.p. 44-48°C;  $[\alpha]_D = -67.3^\circ$  (c 0.26,  $\text{CHCl}_3$ )

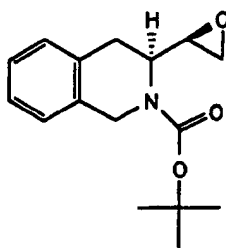
5 Mass Spec. 444 (M+H)

Anal. Calc. for $\text{C}_{22}\text{H}_{41}\text{N}_3\text{O}_6 \cdot 0.56 \text{ H}_2\text{O}$ :			
	C, 58.24;	H, 9.36;	N, 9.26
Found:	C, 58.50;	H, 9.63;	N, 9.00

### Example 9

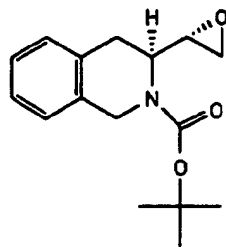
15 Preparation of [S-(R\*,R\*)]-3,3-[[Phenylmethyl]imino]bis(1-hydroxy-2,1-ethanediyl)]bis[2(1H)-isoquinolinecarboxylic acid, bis(1,1-dimethylethyl) ester (Compound 9b)

#### (a) Compound 9a(i)

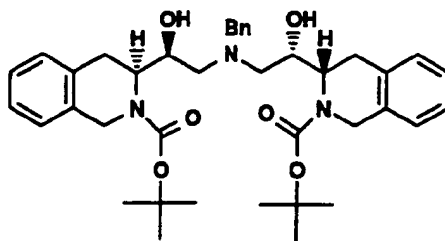


and

#### Compound 9a(ii)



45 Compounds 9a(i) (major) and 9a(ii) (minor) were prepared by a procedure analogous to the synthesis of Compounds 1b(i) and 1b(ii) in which Boc-(L)-tetrahydroisoquinoline-2-carboxylic acid (see *J. Am. Chem. Soc.*, 70, 180 (1948); *ibid* 84, 4487 (1962)) was employed in place of N-Boc-L-phenylalanine.

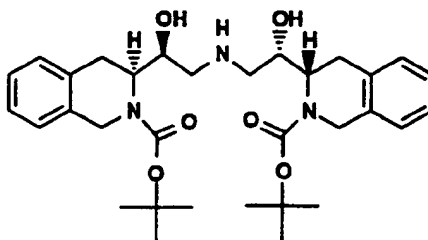
(b) Compound 9b

Compound 9a(i) was converted to the title Compound 9b (light-yellow oil) by opening with 2 equivalents of benzyl amine and then reacting with another molecule of 9a(i) analogous to the two-step procedure used for the preparation of Compound 4b.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.43-1.46 (brs's, 18H), 2.45 (m, 4H), 2.61 (m, 2H), 2.87 (m, 2H), 3.43 (m, 1H), 3.55 (m, 3H), 4.22 (m, 4H), 4.71 (m, 2H), 7.00-7.25 (m, 13H).

Example 10

Preparation of [S-(R\*,R\*)]-3,3'-[Iminobis(1-hydroxy-2,1-ethanediy)]-bis[2(1H)-isoquinolinecarboxylic acid], bis(1,1-dimethylethyl) ester (Compound 10)



Compound 9b was deprotected by a procedure analogous to that used for Compound 7 to give the title Compound 10 (white solid).

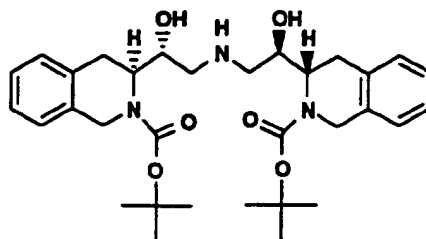
mp 70-76°C; [α]<sub>D</sub> = + 33.6 ° (c 0.25, MeOH);

Mass Spec: 568 (M + H)

Analysis calc. for C <sub>32</sub> H <sub>45</sub> N <sub>3</sub> O <sub>8</sub> ·0.69H <sub>2</sub> O:			
	C, 66.25;	H, 8.06;	N, 7.24;
Found:	C, 66.45;	H, 7.96;	N, 7.04.

Example 11

Preparation of [R-(R\*,R\*)]-3,3'-[Iminobis(1-hydroxy-2,1-ethanediy)]-bis[2(1H)-isoquinolinecarboxylic acid], bis(1,1-dimethylethyl) ester (Compound 11)



Compound 11 (white solid) was prepared from Compound 9a(ii) by procedures analogous to those used for the synthesis of Compound 10.

mp 68-76°C;  $[\alpha]_D^{25} = +34.0^\circ$  (c 0.05, MeOH).

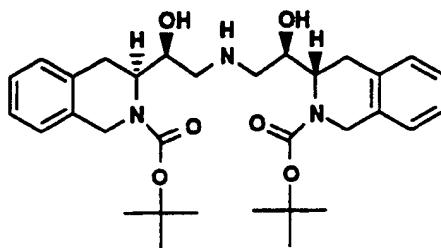
Mass Spec.: 568 (M + H)

Analysis calc. for  $C_{32}H_{46}N_3O_6 \cdot 0.91H_2O$ :

	C, 65.81;	H, 8.08;	N, 7.19;
Found:	C, 65.96;	H, 8.15;	N, 7.04.

### Example 12

Preparation of [S-(R\*,R\*)]-3-[2-[[[S-(R\*,S\*)]-2-[2-[(1,1-Dimethylethoxy)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolyl]-2-hydroxyethyl]amino]-1-hydroxyethyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylic acid, (1,1-dimethylethyl) ester (Compound 12)



Compounds 9a(i) and 9a(ii) were converted to the title Compound 12 (white solid) by procedures analogous to those used for the synthesis of Compound 10 except that epoxide 9a(i) was opened with benzyl amine and the resulting product was reacted with epoxide 9a(ii) by a procedure analogous to that used for Compound 4b.

mp 65-72 °C;  $[\alpha]_D^{25} = +20.5^\circ$  (c 0.19, MeOH).

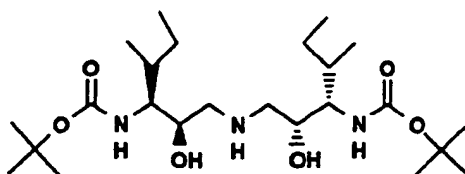
Mass Spec.: 568 (M + H)

Analysis calc. for  $C_{32}H_{45}N_3O_6 \cdot 1.13H_2O$ :

	C, 65.35;	H, 8.10;	N, 7.15;
Found:	C, 65.68;	N, 7.94;	N, 6.82.

### Example 13

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(1-methylpropyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl ester (Compound 13)



Starting from N-Boc-L-isoleucine in place of N-Boc-L-phenylalanine, the title Compound 13 (colorless oil) was prepared using procedures analogous to those described for Compounds 1b(i), 4b, and 7.

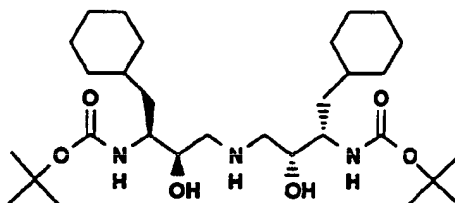
TLC,  $R_f=0.10$ ,  $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$ , 95.5:4.9:0.1, (PMA).

$^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ ):  $\delta$  12.1, 16.7, 24.1, 28.8, 36.1, 52.8, 59.6, 69.6, 80.1, 158.9.

Mass Spec.  $(\text{M}+\text{H})^+$  @ 476

#### Example 14

Preparation of [R-(R\*,S\*)]-[iminobis[1-(cyclohexyl-methyl)-2-hydroxy-3,1-propanediyl]]-biscarbamic acid, bis(1,1-dimethylethyl) ester (Compound 14)



Starting from N-Boc-L-cyclohexylalanine in place of N-Boc-L-phenylalanine, the title Compound 14 (white solid) was prepared using procedures analogous to those described for Compounds 1b(i), 4b, and 7.

$[\alpha]_D = -33.7^\circ$  (c 0.18, MeOH).

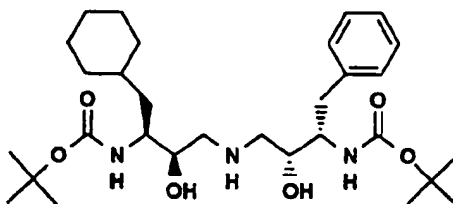
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  26.1, 26.4, 26.5, 28.4, 32.3, 34.2, 34.3, 38.1, 51.0, 51.6, 72.7, 79.5, 156.4.

Mass Spec.  $(\text{M} + \text{H})^+$  @ 556.

High Resolution FAB; exact mass calcd. for  $\text{C}_{30}\text{H}_{58}\text{O}_8\text{N}_3$   $(\text{M} + \text{H})^+$ , 556.4325; Found 556.4304.

#### Example 15

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[4-Cyclohexyl-3-[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-butyl]amino-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 15)



Compound 4a and the epoxide prepared in Example 14 (i.e., in the step analogous to that for Compound 1b(i)) were converted to the title Compound 15 by procedures analogous to those used for Compounds 4b and 7.

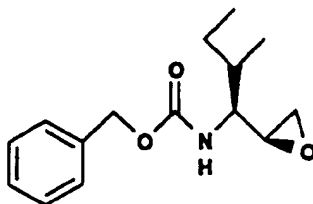
mp  $120-125^\circ\text{C}$ ;  $[\alpha]_D = -15.0^\circ$  (c 0.10, MeOH).

Mass Spec.  $(\text{M} + \text{H})^+$  @ 550.

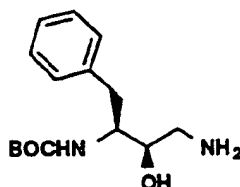
Analysis calc. for $C_{30}H_{51}N_3O_6 \cdot 0.32H_2O$ :			
	C, 64.99;	H, 9.20;	N, 7.58;
Found:	C, 65.08;	H, 9.46;	N, 7.49.

**Example 16**

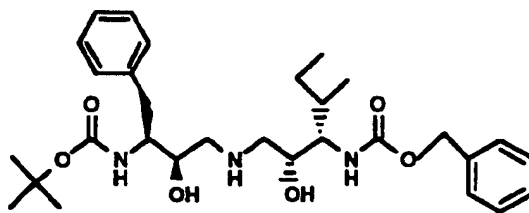
Preparation of [2S-[2R\*,1S\*(2S\*,3R\*)]]-[1-Hydroxy-3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]ethyl-2-methylbutyl]carbamic acid, phenylmethyl ester (Compound 16c)

**(a) Compound 16a**

Compound 16a was prepared by procedures analogous to those used for the synthesis of Compound 1b(i) in which N-Cbz-L-isoleucine was employed in place of N-Boc-L-phenylalanine.

**(b) Compound 16b**

Compound 1b(i) (15.0 g; 56.96 mmol) dissolved in 350 ml of EtOH was added, with stirring, over 1 h to 350 ml of concentrated  $NH_4OH$  at  $0^\circ C$ .  $NH_3$  gas was bubbled through the reaction mixture during the addition and for 1 h after. The reaction was then warmed to RT and stirred overnight. The resulting slurry was diluted with 800 ml EtOAc and the organic layer washed repeatedly with brine. The organic extracts were dried ( $MgSO_4$ ) and concentrated to give a white solid which was triturated with 10% i-PrOH/EtOAc to give 4.37 g of Compound 16b. The mother liquors were evaporated and triturated again as above to give an additional 5.73 g of Compound 16b (total yield: 10.1 g; 63%).

**(c) Compound 16c**

Compounds 16a and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 16c.  
mp  $155-157^\circ C$ ;  $[\alpha]_D = +1.36^\circ$  (c 0.22, MeOH).

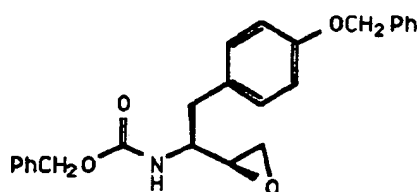
Mass Spec. (M + H)<sup>+</sup> @ 544.

Analysis calc. for C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>6</sub> ·0.38H <sub>2</sub> O			
	C, 65.46	H, 8.38	N, 7.63
Found:	C, 65.48	H, 8.29	N, 7.61

### Example 17

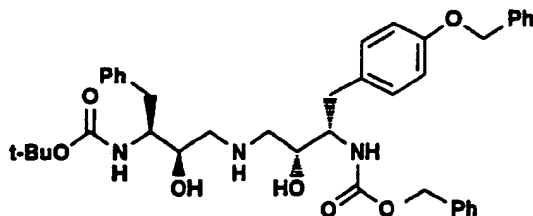
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-(phenylmethoxy)phenyl]methyl]propyl]carbamic acid, phenylmethyl ester (Compound 17b)

#### (a) Compound 17a



Compound 17a was prepared by procedures analogous to those used for the synthesis of Compound 1b(i) where N-Cbz-O-benzyl-L-tyrosine was employed in place of N-Boc-L-phenylalanine.

#### (b) Compound 17b



Compounds 17a and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 17b.

m.p.: 154-155.5°C.

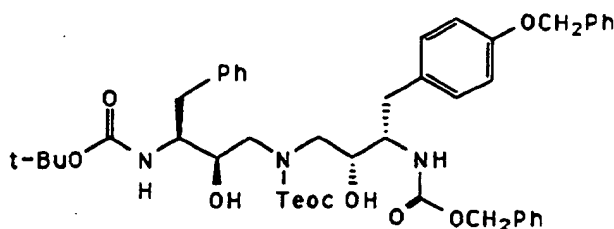
[α]<sub>D</sub> = 19.09° (c 0.24, DMSO).

MS (FAB): 684<sup>+</sup> (M+H)<sup>+</sup>.

Anal. Calc. for C<sub>40</sub>H<sub>49</sub>N<sub>3</sub>O<sub>7</sub>·0.87H<sub>2</sub>O: C, 68.68; H, 7.31; N, 6.01. Found: C, 68.84; H, 7.18; N, 5.85.

### Example 18

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-[[4-(phenylmethoxy)phenyl]methyl]propyl]carbamic acid, phenylmethyl ester (Compound 18)

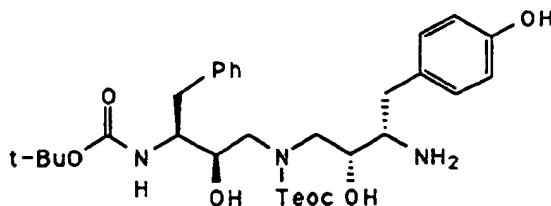


To the mixture of Compound 17b (342 mg, 0.5 mmol) and  $i\text{-Pr}_2\text{NEt}$  (140  $\mu\text{l}$ , 0.8 mmol) in dry DMF (3.8 ml) cooled at  $0^\circ\text{C}$  was added 2-trimethylsilylethyl chloroformate (125  $\mu\text{l}$ , 0.55 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 1.0 hr and diluted with EtOAc (70 ml).  $\text{H}_2\text{O}$  (50 ml) was added and the mixture was extracted with additional EtOAc (2 x 20 ml). The combined organic layers were washed with saturated  $\text{NaHCO}_3$  (40 ml) and brine (40 ml) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration *in vacuo* followed by flash chromatography (100%  $\text{CHCl}_3$  to 2:1  $\text{CHCl}_3$ -EtOAc) afforded 401 mg (97%) of Compound 18 as a white foam.

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ): 7.17-7.44 (m, 15H), 7.08 (d,  $J = 8.12$ , 2H), 6.85 (d,  $J = 8.12$ , 2H), 4.99 (s, 2H), 4.58 and 4.72 (bs, 2H), 4.14 (t,  $J = 8.77$ , 2H), 3.70-4.00 (m, 4H), 3.15-3.55 (m, 4H), 2.70-3.00 (m, 4H), 1.32 (s, 9H), 0.94 (m, 2H), 0.00 (s, 9H).

#### Example 19

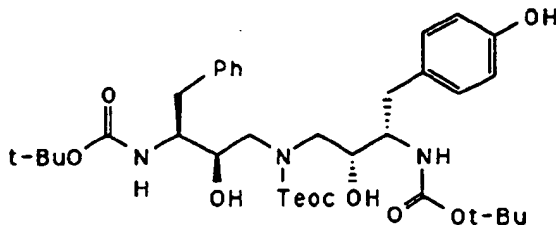
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[3-Amino-2-hydroxy-4-(4-hydroxyphenyl)butyl]][[2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 19)



To the solution of Compound 18 (401 mg, 0.485 mmol) in 17 ml of 100% EtOH was added 200 mg of  $\text{Pd}(\text{OH})_2$ . The mixture was stirred under a  $\text{H}_2$  atmosphere overnight (>16 hrs). The catalyst was removed by filtration through a small plug of Celite and washed several times with MeOH. Concentration *in vacuo* afforded an oily residue, which after recrystallization from  $\text{CHCl}_3$  (2.0 ml) and hexane (25 ml) gave 272 mg (93%) of Compound 19 as an off-white solid. This material was immediately used in the next Example.

#### Example 20

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-hydroxyphenyl)butyl]][[2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 20)

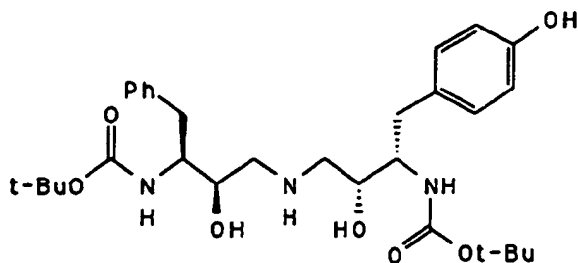


To the solution of Compound 19 (121 mg, 0.20 mmol) in 1,4-dioxane-water (1:1, 0.6 ml) was added  $\text{Et}_3\text{N}$

(42  $\mu$ l, 0.30 mmol), followed by Boc-ON (59 mg, 0.24 mmol). The mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (25 ml) and washed with H<sub>2</sub>O (2 x 10 ml). The aqueous layer was extracted with EtOAc (2 x 25 ml). The combined organic layers were washed with saturated NaHCO<sub>3</sub> (20 ml) and brine (20 ml) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (100% CHCl<sub>3</sub> to 95:5 CHCl<sub>3</sub>-MeOH) on a silica gel column (190 x 20 mm) afforded 132 mg of Compound 20 as a glassy solid, which was triturated with hexane to give 126 mg (94%) of Compound 20 as a white solid. MS (FAB): 704<sup>+</sup> (M+H)<sup>+</sup>.

#### Example 21

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-hydroxyphenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 21)



The mixture of Compound 20 (124 mg, 0.176 mmol) and solid *n*-Bu<sub>4</sub>NF·nH<sub>2</sub>O (138 mg, 0.529 mmol) in dry THF (0.75 ml) was heated at 50°C for 4.0 hrs. After cooling to room temperature, Celite (1.0 g) was added and the solvent was removed under reduced pressure. Flash chromatography (100% CHCl<sub>3</sub> to CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH: 92:8:0.8) on silica gel column (20 x 200 mm) afforded 79 mg (81%) of Compound 21 as a white solid. m.p.: 151.0-152.5°C.

$[\alpha]_D^{25} = -1.53^\circ$  (c 0.196, CHCl<sub>3</sub>).

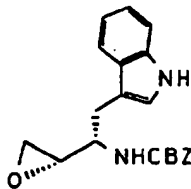
MS (FAB): 560<sup>+</sup> (M+H)<sup>+</sup>.

Anal. Calc. for C<sub>30</sub>H<sub>45</sub>N<sub>3</sub>O<sub>7</sub>·0.70H<sub>2</sub>O: C, 62.96; H, 8.17; N, 7.34. Found: C, 63.03; H, 8.08; N, 7.27.

#### Example 22

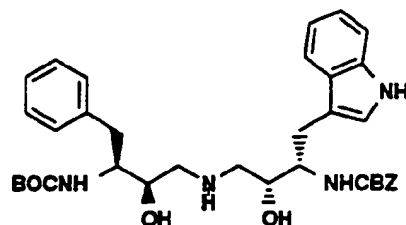
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[(1H-indol-3-yl)methyl]propyl]carbamic acid, phenylmethyl ester (Compound 22b)

##### (a) Compound 22a



Compound 22a was prepared by procedures analogous to those used for the synthesis of Compound 1b(i) in which N-Cbz-L-tryptophan was employed in place of N-Boc-L-phenylalanine.



(b) Compound 22b

Compounds 22a and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 22b (white solid).

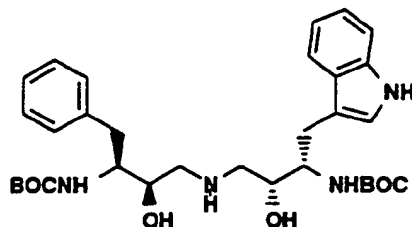
Elemental Analysis (%) $C_{35}H_{44}N_4O_6 \cdot 0.89$ $H_2O$		
	Calc.	Found
C	67.62	67.53
H	7.22	7.14
N	9.01	9.10

m.p. 170 - 171°C

$[\alpha]_D = 21.1^\circ$  (c = 0.48, MeOH)

Example 23

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(1H-indol-3-ylmethyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 23)



Compound 22b was converted to the title Compound 23 (white solid) using procedures analogous to those for the synthesis of Compounds 18 through 21 (di-tert-butylidicarbonate was used instead of BOC-ON to put on the Boc group).

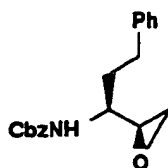
Elemental Analysis (%) for $C_{32}H_{48}N_4O_8 \cdot 1.09 H_2O$		
	Calc.	Found
C	65.24	65.31
H	7.99	8.18
N	9.51	9.44

m.p. 168 - 169°C  
 $[\alpha]_D = -14.4^\circ$  (c=0.21, MeOH)

#### Example 24

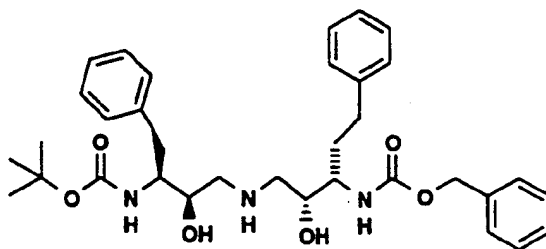
Preparation of [1S-[1R\*,2S\*((2S\*,3R\*))]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(2-phenylethyl)propyl]carbamic acid, phenylmethyl ester (Compound 24b)

##### (a) Compound 24a



Compound 24a was prepared by procedures analogous to those used for the synthesis of Compound 1b(i), in which N-Cbz-L-homophenylalanine was employed in place of N-Boc-L-phenylalanine.

##### (b) Compound 24b



Compounds 24a and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 24b.

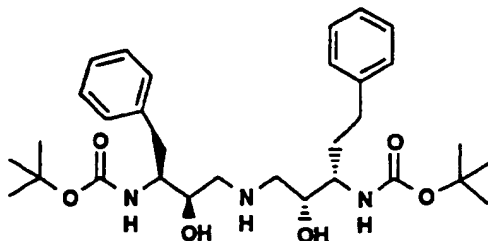
mp 150-151°C.  $[\alpha]_D = -9.1^\circ$  (c 0.2, MeOH).

Mass Spec.  $[M+H]^+ = 592$ .

Analysis calc. for $C_{34}H_{46}N_3O_8 \cdot 0.43 H_2O$ :			
	C, 68.13;	H, 7.71;	N, 7.01;
Found:	C, 68.15;	H, 7.58;	N, 6.99.

## Example 25

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(2-phenylethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 25)



Compound 24b was converted to the title Compound 25 using procedures analogous to those for the synthesis of Compounds 18 through 21.

mp 145 - 148°C;  $[\alpha]_D = -6^\circ$  (c 0.3, MeOH).

Mass Spec: Fab (M + H)<sup>+</sup>: 558.

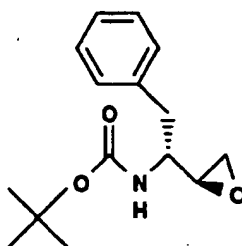
Analysis calculated for C <sub>31</sub> H <sub>47</sub> N <sub>3</sub> O <sub>6</sub> ·0.44H <sub>2</sub> O:			
	C; 65.82;	H; 8.53;	N; 7.43;
Found:	C; 65.69;	H; 8.40;	N; 7.56.

## Example 26

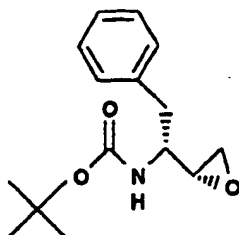
Preparation of [1R-[1R\*,2R\*(2R\*,3S\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 26b(i)) and

Preparation of [1R-[1R\*,2S\*(2R\*,3S\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 26b(ii))

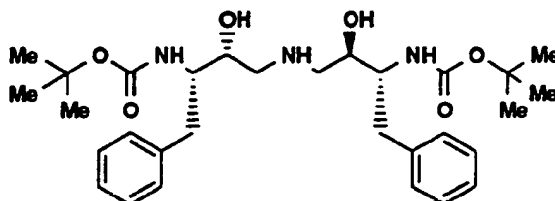
(a) Compound 26a(i)



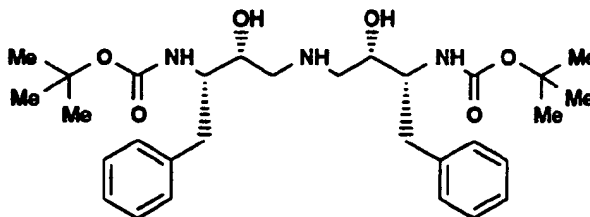
and

Compound 26a(ii)

Compounds 26a(i) and 26a(ii) were prepared by procedures analogous to those used for the synthesis of Compounds 1b(i) and 1b(ii), in which N-Boc-D-phenylalanine was employed in place of N-Boc-L-phenylalanine.

(b) Compound 26b(i)

and

Compound 26b(ii)

A mixture of Compounds 26a(i) and 26a(ii) were reacted with Compound 16b by a procedure analogous to that used for the preparation of Compound 4b (except that MeOH at 55° was used in place of DMF) to give, after separation by silica gel chromatography the title Compounds 26b(i) and 26b(ii).

Compound 26b(i)

m.p. 158-160°C;  $[\alpha]_D^{25} = +14.9^\circ$  (c 0.35, MeOH).

MS: (Cl/NH<sub>3</sub>): 544 (M+H).

Anal. Calc. for C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>8</sub> · 0.67 H <sub>2</sub> O			
	C, 64.84;	H, 8.40;	N, 7.56
Found:	C, 64.66;	H, 8.28;	N, 7.74

Compound 26b(ii)

m.p. 200-201°C;  $[\alpha]_D^{25} = +6.0^\circ$  (c 0.1, DMSO).

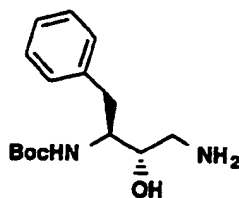
MS: (FAB): 544 (M+H).

Anal. Calc. for $C_{30}H_{45}N_3O_8 \cdot 0.32 H_2O$			
	C, 65.58;	H, 8.37;	N, 7.65
Found:	C, 65.44;	H, 8.38;	N, 7.79

### Example 27

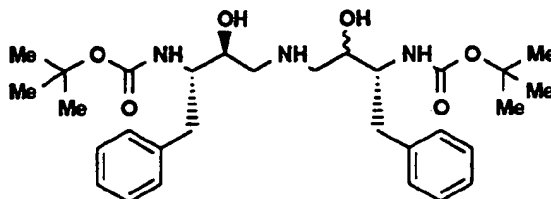
Preparation of [1S-[1R\*,2R\*(3S\*)]]-[3-[[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid 1,1-dimethylethyl ester (Compound 27b)

#### (a) Compound 27a



Compound 1b(ii) was converted to Compound 27a by a procedure analogous to the one used for the preparation of Compound 16b.

#### (b) Compound 27b



A mixture of Compounds 26a(i) and 26a(ii) were reacted with Compound 27a by a procedure analogous to that used for the preparation of Compound 4b (except that MeOH at 55° was used in place of DMF) to give the title Compound 27b as a mixture of diastereomers.

m.p. 156-159°C; MS: (CI/NH<sub>3</sub>): 544 (M+H).

Anal. Calc. for $C_{30}H_{45}N_3O_8 \cdot 0.16 H_2O$			
	C, 65.91;	H, 8.36;	N, 7.69
Found:	C, 65.89;	H, 8.34;	N, 7.71

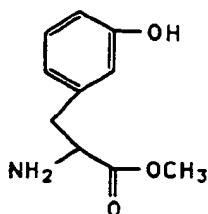
### Example 28

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[3-(phenylmethoxy)phenyl]methyl]propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 28g)

(a) Compound 28a

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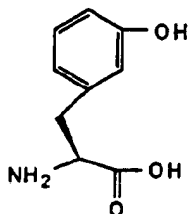


SOCl<sub>2</sub> (1.28 ml) was added dropwise to a solution of DL-meta-tyrosine (3.2 g, 17.7 mmol) in 4.4 ml MeOH at -15°C and the resulting solution was stirred at 0°C for 2 h, and at RT overnight. The reaction mixture was concentrated *in vacuo* and the residue was washed with Et<sub>2</sub>O, filtered, and dried *in vacuo* to yield 3.2 g (94%) of the HCl salt of methyl ester Compound 28a.

(b) Compound 28b

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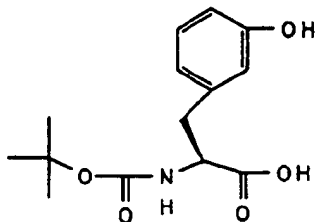


Compound 28a (1.54 g, 6.65 mmol) in 70 ml of 0.2N NaHCO<sub>3</sub> was added to a 100 ml aqueous solution of Subtilisin (protease type VIII from *Bacillus licheniformis*, 3.8 mg) and the reaction mixture was stirred slowly at RT for 40 min. The pH of this solution was maintained at pH 8.0 with the occasional addition of 1N NaOH. Unreacted methyl ester of D-m-tyrosine was extracted 5X with 100 ml portions of EtOAc. The aqueous solution was acidified with 1N HCl to pH 6.0 and concentrated to 5 ml. The resulting solid was filtered, washed with 1 ml of cold H<sub>2</sub>O and dried to yield 0.45 g of Compound 28b. The filtrate was passed through 20 ml of Dowex AG50 in H<sup>+</sup> form, followed by the elution of desired material with 2% pyridine in H<sub>2</sub>O to yield an additional 0.14 g of Compound 28b (total 0.59 g, 98%). This crude product was carried on to the next step.

(c) Compound 28c

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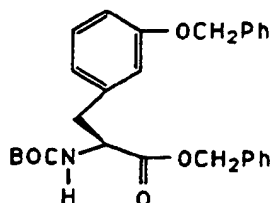


Compound 28b (0.473 g, 2.61 mmol) was reacted with BOC-anhydride (0.613 g, 2.81 mmol) in 20 ml of absolute EtOH overnight at RT. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in EtOAc (400 ml) and washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude product was chromatographed through 80 g of silica gel using a (2:1:97) MeOH:HOAc:CHCl<sub>3</sub> solvent system. The resulting product was crystallized from CHCl<sub>3</sub> (15 ml) to yield 0.41 g (59%) of Compound 28c. [α]<sub>D</sub> = +10.8° (M OH, c=1.0)

(d) Compound 28d

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10



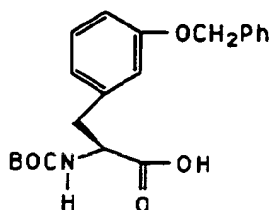
15

Compound 28c (0.41 g, 1.46 mmol), benzyl bromide (0.51 g, 2.98 mmol) and  $\text{Cs}_2\text{CO}_3$  (0.97 g, 2.96 mmol) were stirred in DMF (2.5 ml) overnight. The reaction mixture was diluted with 200 ml of EtOAc and the organic solution was washed with water, brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The product was crystallized from 10 ml of (1:1)  $\text{Et}_2\text{O}$ :hexane to yield 0.54 g (81%) of Compound 28d.

(e) Compound 28e

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25



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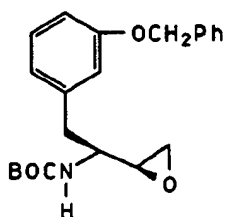
35

Compound 28d (1.147 g; 2.49 mmol) was dissolved in 2.5 ml of THF and 2.5 ml of 1N LiOH and stirred at RT for 20 min. An additional 2.0 ml of THF was added and the reaction was stirred for 40 more min. The reaction mixture was neutralized with 2.5 ml of 1N HCl at 0°C and concentrated *in vacuo* to 4 ml. The product was extracted with EtOAc and this solution was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated *in vacuo*. The residue was redissolved in 50 ml of saturated  $\text{NaHCO}_3$  and washed with  $\text{Et}_2\text{O}$  (3X). The bicarbonate solution was neutralized with 1N HCl and the product was extracted with EtOAc. The organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to yield Compound 28e (0.84 g, 91%).

(f) Compound 28f

40

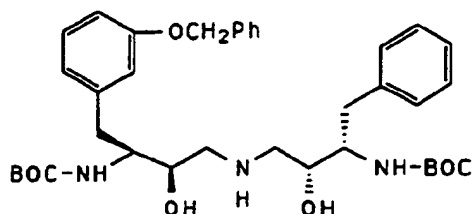
45



50

Compound 28e was converted into Compound 28f by procedures analogous to those used for the synthesis of Compound 1b(i).

55

(g) Compound 28g

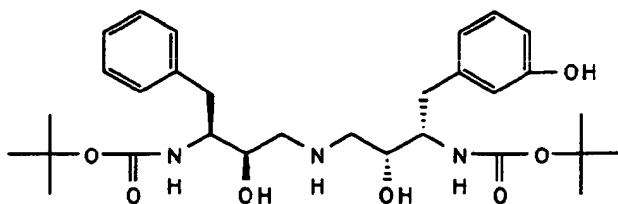
Compounds 28f and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 28g.

mp = 125-145°C.

High Resolution mass spec: (M+H)<sup>+</sup>=650.3802; theory =650.3805.

Example 29

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-(3-hydroxyphenyl)butyl]-amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 29)



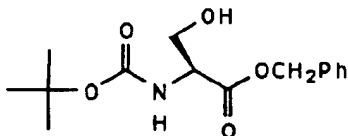
The benzyl group of Compound 28g (0.177 mmol) was removed by hydrogenolysis (MeOH, cat. Pd(OH)<sub>2</sub>, H<sub>2</sub>) by a procedure analogous to that used for the preparation of Compound 7 to give, after silica gel chromatography, 53 mg (51%) of the title Compound 29.

m.p. = 193-196°C, [α]<sub>D</sub> = -5.65° (MeOH, c=0.23)

High Resolution mass spec: (M+H)<sup>+</sup> 560.3343 theory=560.3336.

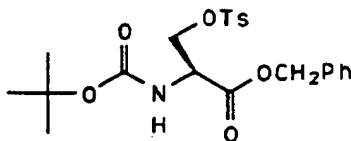
Example 30

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(4-pyridinylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 30g)

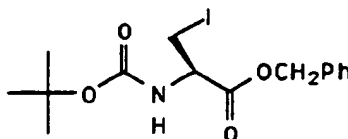
(a) Compound 30a

Boc-L-serine (4.03 g, 19.6 mmol) and benzyl bromide (3.35 g, 19.6 mmol) were stirred with Cs<sub>2</sub>CO<sub>3</sub> (7.5 g, 23.0 mmol) in 20 ml of DMF at 5°C for 4 h. The reaction was diluted with Et<sub>2</sub>O (500 ml) and the resulting mixture was washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The resulting residue solidified and was triturated with hexane, filtered, and dried *in vacuo* to yield Compound 30a as a white solid (mp 62-64°C, 5.02 g, 86%).

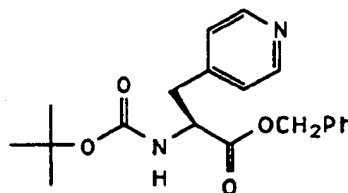


(b) Compound 30b

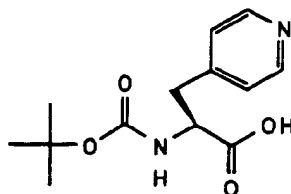
Compound 30a (5.0 g, 16.9 mmol) was dissolved in 10 ml of pyridine, and the reaction was cooled to  $-10^{\circ}\text{C}$ . Tosyl chloride (3.24 g, 17.0 mmol) was added portionwise and the reaction mixture was stirred at  $-10^{\circ}\text{C}$  for 4 h. Crushed ice was added to the reaction mixture which was stirred until the product solidified. The solid was filtered and washed thoroughly with water and finally dried over  $\text{P}_2\text{O}_5$  overnight to give Compound 30b (mp  $88-90^{\circ}\text{C}$ , 6.8 g, 80%).

(c) Compound 30c

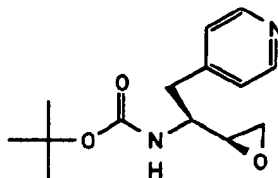
Compound 30b (5.0 g, 11.12 mmol) was partially dissolved in 26 ml of acetone. NaI (1.9 g, 12.75 mmol) was added and the reaction mixture was stirred for 48 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was chromatographed on 200 g of silica gel using (5:95) acetone:hexane to give Compound 30c as a white solid (mp  $78-80^{\circ}\text{C}$ , 3.6 g, 82%).

(d) Compound 30d

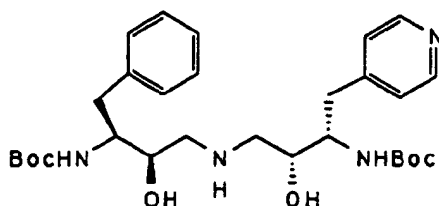
Three grams of zinc dust and 3 g of copper (II) acetate monohydrate were suspended in 6 ml of glacial HOAc and this mixture was stirred until it solidified (15 min). The mixture was triturated with  $\text{Et}_2\text{O}$  and transferred to a filter funnel under a stream of argon. The solid was washed with  $\text{Et}_2\text{O}$  (200 ml) followed by benzene (50 ml). The resulting Zn/Cu couple reagent was dried *in vacuo* over  $\text{P}_2\text{O}_5$  for 2 h; 0.54 g of it was suspended in 3 ml of benzene and 0.6 ml of dimethylacetamide, and sonicated while a solution of Compound 30c (1.82 g, 4.06 mmol) in 7 ml of benzene was added slowly. The reaction mixture was sonicated for 45 min and then diluted with 4 ml of benzene. 4-Bromopyridine (0.64 g, 4.06 mmol) and  $\text{Pd}((\text{Ph})_3\text{P})_2\text{Cl}_2$  (0.23 g) was added and the reaction mixture was stirred at  $40^{\circ}\text{C}$  for 1 h. The reaction mixture was diluted with  $\text{EtOAc}$  (200 ml) and filtered. The filtrate was stirred with 50 ml of 0.1N HCl then neutralized with saturated  $\text{NaHCO}_3$ . The organic layer was separated, washed with  $\text{H}_2\text{O}$ , brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude product was chromatographed on 80 g of silica gel using (2:8) acetone:hexane to give Compound 30d (0.71 g, 49%).

(e) Compound 30e

Compound 30d (1.2 mmol) was saponified with aqueous LiOH (1.3 ml of 1N solution) in 1.2 ml THF using a procedure analogous to the one used for Compound 28e to give 0.28 g of the title Compound 30e (m.p. = 218°C)

(f) Compound 30f

Compound 30e was converted into Compound 30f by procedures analogous to those used for the synthesis of Compound 1b(i).

(g) Compound 30g

Compounds 30f and 16b were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 30g.

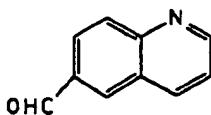
High Resolution mass spec(M+H)<sup>+</sup> 545.3347<sup>+</sup>

Theoretical (M+H)<sup>+</sup> 545.3339<sup>+</sup>

<sup>1</sup>H (CD<sub>3</sub>OD, 300MHz, 50°C): δ 8.39-8.37 (m, 2H), 7.31-7.14 (m, 7H), 3.76-3.59 (m, 4H), 3.05-3.27 (m, 2H), 2.60-2.85 (m, 6H), 1.29 (br s, 9H).

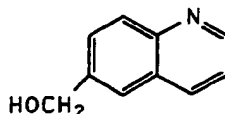
Example 31

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino-2-hydroxy-1-(6-quinolinylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 31i)

(a) Compound 31a

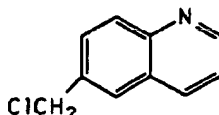
6-Methylquinoline (7.0 g, 49 mmol) and selenium oxide (6.0 g, 54 mmol) were heated at 150°C for 1 h and at 220°C for 30 min. The reaction mixture was cooled to RT and the residue was triturated with MeOH and filtered. The filtrate was concentrated *in vacuo*, and the crude product was chromatographed on 250 g of silica gel using 3:7 EtOAc:Hexane. The appropriate fractions were combined and concentrated to yield 3.8 g (49%) of Compound 31a as a white solid. m.p. 93-95°C

(b) Compound 31b



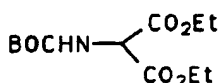
Compound 31a (1.65 g, 10.5 mmol) was dissolved in 50 ml of MeOH, cooled to 5°C and NaBH<sub>4</sub> (0.397g, 10.5 mmol) was added and the reaction mixture was stirred for 15 min. After the addition of 10 ml saturated NH<sub>4</sub>Cl, the reaction mixture was concentrated to 10 ml and extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to yield a viscous oil which on standing solidified (74-78°C). This material was dissolved in Et<sub>2</sub>O and 4N HCl was added until acidic. The HCl salt that precipitated was filtered and dried to yield 1.56 g (76%) of Compound 31b as its hydrochloride salt.

(c) Compound 31c



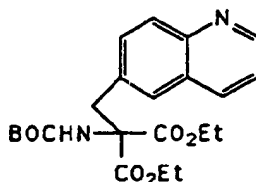
SOCl<sub>2</sub> (4.5 ml) was added to Compound 31b (1.46 g, 7.5 mmol). The reaction mixture was heated at 110°C for 1 h, and excess SOCl<sub>2</sub> was distilled off. The residue was dissolved in H<sub>2</sub>O and 1N KOH was added until basic (pH 12). The product was extracted with EtOAc and this solution was washed with H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield Compound 31c (1.22 g, 91%) as a crystalline solid. m.p. 65-68°C.

(d) Compound 31d



Diethylaminomalonate (4.23 g, 20 mmol), di-tert-butylidicarbonate (4.4 g, 20 mmol) and Et<sub>3</sub>N (2.8 ml, 20 mmol) were dissolved and stirred in 150 ml of absolute EtOH for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (300 ml). This was washed with aqueous KHSO<sub>4</sub> (10%), brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to yield Compound 31d (4.3 g, 78%) as an oil.

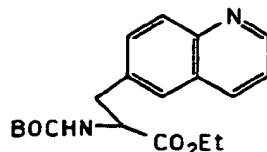
(e) Compound 31e



Sodium ethoxide (4.27M in EtOH, 3.0 ml, 12.8 mmol) was added to an EtOH (5 ml) solution of Compound 31d (3.52 g, 12.8 mmol), followed by the addition of Compound 31c (1.13 g, 6.4 mmol). The reaction mixture

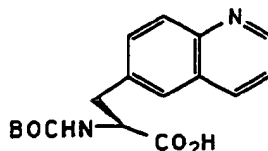
was refluxed for 3.5 h. Celite (2 g) was added and the mixture was concentrated and chromatographed on 80 g of Merck silica gel to yield Compound 31e (2.03 g, 76%) as a crystalline solid. m.p. 110-113°C

5 (f) Compound 31f



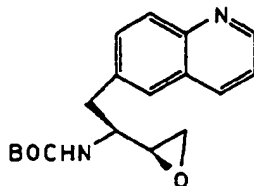
15 Compound 31e (0.8 g, 1.9 mmol) was dissolved in 1 ml of THF and 2.2 ml of 1N LiOH. The reaction mixture was stirred at 40°C for 4 hr, concentrated down to 2 ml and HOAc was added until pH 4 was reached. The mono-acid precipitated and was filtered. Without further purification this material was suspended in dioxane and the reaction mixture was heated at reflux for 2 hr. The reaction was concentrated and the resulting residue was chromatographed on 50 g of Merck silica gel using (3:7) acetone:hexane to afford Compound 31f (0.52 g, 80%). m.p. 92-95°C

20 (g) Compound 31g



30 Compound 31f (1.8 g, 5.2 mmol) in 45 ml of DMF was added dropwise to 700 ml of H<sub>2</sub>O containing 10 mg of Subtilisin protease VII and 50 ml of 0.2N NaHCO<sub>3</sub>. After the addition, the pH was maintained at 7.5 to 8.0 with the occasional addition of 0.1N NaOH. After 2.5 h the solution was extracted with EtOAc and the aqueous layer was acidified to pH 4 with HOAc. The aqueous layer was concentrated *in vacuo* and the crude product was chromatographed on 80 g of Merck silica gel using 16:1.5:0.25 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:HOAc to afford Compound 31g (0.82 g, 90%). m.p. 184-189°C (dec)  
35 [α]<sub>D</sub> = +29.0° (c 0.77, MeOH)

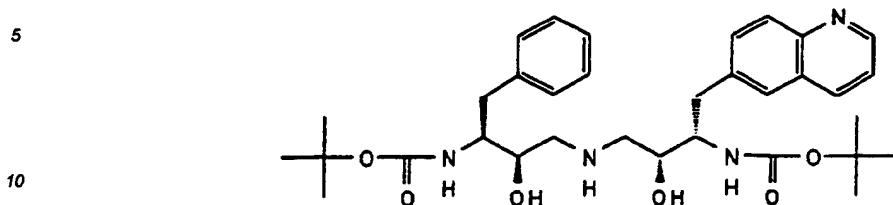
(h) Compound 31h



50 Compound 31h was prepared from Compound 31g by a multi-step procedure analogous to that used for the conversion of N-Boc-L-phenylalanine to Compound 1b(i). m.p. 136-140°C

55

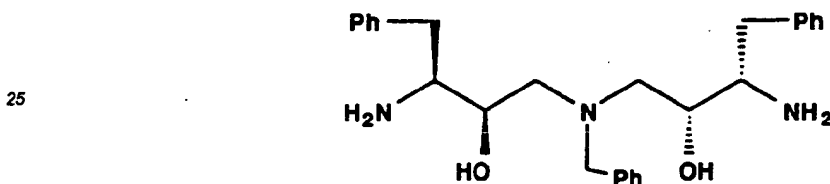
**(i) Compound 31i**



Compound 31h (100.9 mg, 0.321 mmol) was reacted with Compound 16b (90 mg, 0.321 mmol) by a procedure analogous to that of Example 4b to afford the title Compound 31i (0.113 g; 59%) as a white solid. m.p. 105-112°C;  $[\alpha]_D^{25} = +4.55^\circ$  (c 0.88, MeOH).

### Example 32

20 Preparation of [2R-(2R\*,3S\*)]-1,1'-(Phenylmethyl)iminobis(3-amino-4-phenyl-2-butanol)hydrochloride salt  
(Compound 32)

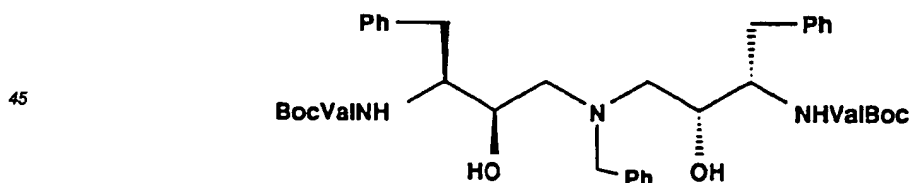


30 To neat Compound 1c (117 mg, 0.185 mmol) at 0°C was added HCl in dioxane (2.0 mL, 4 M). The reaction mixture was stirred at 0°C for 15 min and then 1.15 h at RT. The volatiles were then removed *in vacuo* and the residue co-evaporated with dry Et<sub>2</sub>O. The resulting solid was dried under high vacuum (P<sub>2</sub>O<sub>5</sub>) for 4 h to give the title Compound 32 as a colorless solid (91 mg), which was used without further purification as the tri-HCl salt.

35  $R_f = 0.53$  (20:7:80, MeOH:NH<sub>4</sub>OH:CHCl<sub>3</sub>)

### Example 33

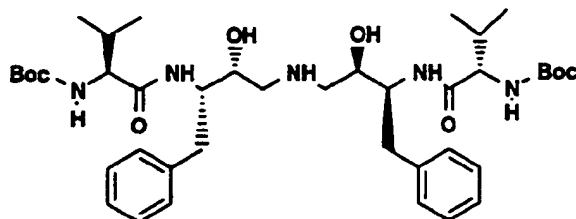
40 Preparation of [S-(1R',2S'')-N,N'-[(Phenylmethyl)iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis-  
[N2-[(1,1-dimethylethoxy)carbonyl]-L-valinamide] (Compound 33)



To a solution of Compound 32 ( $\cong 0.185$  mmol) and Boc-(L)-valine (87 mg, 0.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) at  $0^\circ\text{C}$  under argon was added EDCI (85 mg, 0.44 mmol), HOBT (93 mg, 0.69 mmol), and 4-methylmorpholine (0.065 mL). After 20 min at  $0^\circ\text{C}$ , the reaction mixture was stirred at RT for 68 h. The reaction mixture was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ . The organic layer was extracted with brine, dried over  $\text{Na}_2\text{SO}_4$ , and the volatiles were evaporated *in vacuo* to give an oily-solid residue. This residue (140 mg) was purified by flash column chromatography (silica gel, 2.5 by 13 cm), eluting with 0.5, 1, 2, 3, 4 and then 12% M OH: $\text{CH}_2\text{Cl}_2$  to give the title Compound 33 (29.6 mg, 19% yield for the 2 steps) as a colorless solid.  $R_f = 0.59$  (15% M OH: $\text{CH}_2\text{Cl}_2$ ).

**Example 34**

Preparation of [S-(1R\*,2S\*)]-N,N'-[[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[N<sup>2</sup>-[(1,1-dimethylethylethoxy)carbonyl]-L-valinamid]] (Compound 34)



Compound 33 was converted to the title Compound 34 by a procedure analogous to the one used for the synthesis of Compound 7.

m.p. 216-222°C;  $[\alpha]_D^{25} = -28.55^\circ$  (c 0.16, MeOH).

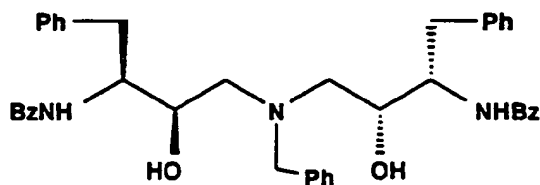
MS: 742 (M+H).

Anal. Calc. for  $C_{40}H_{63}N_5O_8 \cdot 0.27 H_2O$ :

	C, 64.32;	H, 8.58;	N, 9.38
Found:	C, 63.90;	H, 8.49;	N, 9.80

**Example 35**

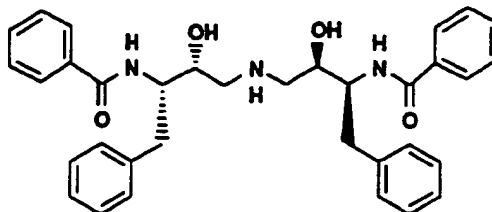
Preparation of [S-(1R\*,2S\*)]-N,N'-[[[(Phenylmethyl)imino]bis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bisbenzamide] (Compound 35)



To a suspension of Compound 32 ( $\approx 0.168$  mmol) in  $CH_2Cl_2$  (1.5 mL) was added *i*-Pr<sub>2</sub>NEt (0.09 mL), resulting in a homogeneous solution. To the stirring reaction mixture at 0°C was added 0.04 ml of benzoyl chloride. A second portion of  $CH_2Cl_2$  (1.5 mL) and *i*-Pr<sub>2</sub>NEt (0.09 mL) was added after 30 min at 0°C and the reaction mixture was stirred at RT for 1.5 h. At 0°C, the reaction mixture was quenched with saturated NaHCO<sub>3</sub> and the aqueous layer was saturated with NaCl and extracted with EtOAc and  $CH_2Cl_2$ . The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and the volatiles were evaporated *in vacuo* to a slightly yellow solid residue which was purified by silica gel chromatography (2 by 10 cm), eluting with 8:2 EtOAc: $CH_2Cl_2$ , then EtOAc to give the title Compound 35 (96 mg, 93% yield) as a colorless solid.  $R_f = 0.60$  (20:7:80 MeOH:NH<sub>4</sub>OH:CHCl<sub>3</sub>).

**Example 36**

Preparation of [S-(1R\*,2S\*)]-N,N'-[[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bisbenzamide] (Compound 36)



A mixture of Compound 35 (96 mg, 0.157 mmol) and  $\text{Pd}(\text{OH})_2$  (45 mg, 20% on carbon) in aqueous HOAc (3 mL, 90%) at RT was stirred under a  $\text{H}_2$  atmosphere. After 7 h, a second portion of  $\text{Pd}(\text{OH})_2$  (6 mg) was added. The reaction mixture was stirred for an additional 45 min and filtered through Celite, washing the filter pad thoroughly with aqueous HOAc. The volatiles were removed *in vacuo* to give a colorless solid which was triturated twice with hot  $\text{Et}_2\text{O}$  and once with hot  $\text{EtOAc}$ . The resulting residue was purified by flash chromatography (silica gel, 1 by 11 cm), eluting with  $\text{MeOH}:\text{NH}_4\text{OH}:\text{CH}_2\text{Cl}_2$  (1:0.1:9) to give the title Compound 36 (50 mg, 58% yield) as a colorless solid.

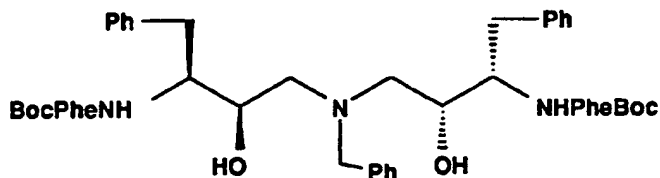
m.p. dec. 227-231°C;  $[\alpha]_{\text{D}}^{25} = -83.95^\circ$  (c 0.21, DMSO); MS: 552 (M+H).

Anal. Calc. for  $\text{C}_{34}\text{H}_{37}\text{N}_3\text{O}_4$ :

	C, 74.02;	H, 6.76;	N, 7.62
Found:	C, 73.88;	H, 6.70;	N, 7.62

#### Example 37

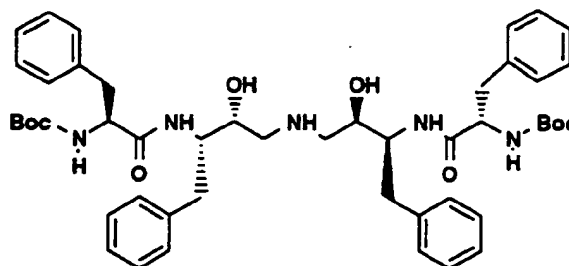
Preparation of [S-(1R\*,2S\*)]-[[(Phenylmethyl)imino]bis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bisiminobis[N<sup>2</sup>-[(1,1-dimethylethoxy)carbonyl]-L-phenylalaninamide] (Compound 37)



Compound 32 was coupled with Boc-L-phenylalanine by a procedure analogous to the one used for the synthesis of Compound 33 (1:1  $\text{CH}_2\text{Cl}_2$ :DMF was used) to give the title Compound 37.  $R_f = 0.78$  (10%  $\text{MeOH}:\text{CH}_2\text{Cl}_2$ ).

#### Example 38

Preparation of [S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]-bisiminobis[N<sup>2</sup>-[(1,1-dimethylethoxy)carbonyl]-L-phenylalaninamide] (Compound 38)



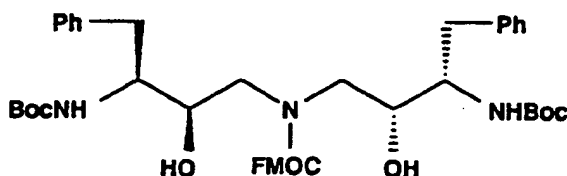
Compound 37 was converted to the title Compound 38 by a procedure analogous to the one used for the synthesis of Compound 36. m.p. dec. 206-212°C;  $[\alpha]_D^{25} = -14.28^\circ$  (c 0.13, DMSO); MS: (CI/NH<sub>3</sub>): 838 (M+H).

Anal. Calc. for C<sub>48</sub>H<sub>63</sub>N<sub>5</sub>O<sub>8</sub> · 1.07 H<sub>2</sub>O:

	C, 67.24;	H, 7.66;	N, 8.17
Found:	C, 67.23;	H, 7.26;	N, 8.18

### Example 39

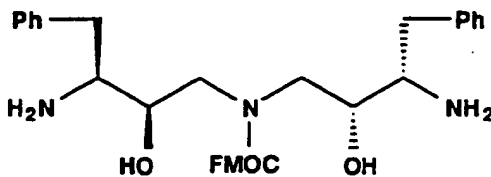
Preparation of [S-(1R\*,2S\*)]-N,N'-[[[(9H-Fluoren-9-ylmethoxy)carbonyl]imino]-bis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, bis(1,1-dimethylethyl) ester (Compound 39)



To a mixture of Compound 2 (192 mg, 0.354 mmol) in i-Pr<sub>2</sub>NEt (0.08 mL) and DMF (2 mL) at 0°C was added 9-fluorenylmethyl chloroformate (100 mg, 0.386 mmol). After 1 h at 0°C, the reaction mixture was stirred at RT for 2 h, quenched at 0°C with saturated NaHCO<sub>3</sub>, and extracted with EtOAc. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the volatiles removed *in vacuo* to leave an oily-foam which was purified by flash chromatography (silica gel, 2.5 by 12 cm), eluting with 30% EtOAc:CH<sub>2</sub>Cl<sub>2</sub> to give the title Compound 39 (251 mg, containing 8% by weight of EtOAc by <sup>1</sup>H NMR analysis, 85% yield) as an oily foam. R<sub>f</sub> = 0.33 (35:65, EtOAc:CH<sub>2</sub>Cl<sub>2</sub>).

### Example 40

Preparation of [R-(R\*,S\*)]-N,N-Bis(3-amino-2-hydroxy-4-phenylbutyl)carbamic acid, 9H-fluoren-9-ylmethyl ester, hydrochloride salt (Compound 40)

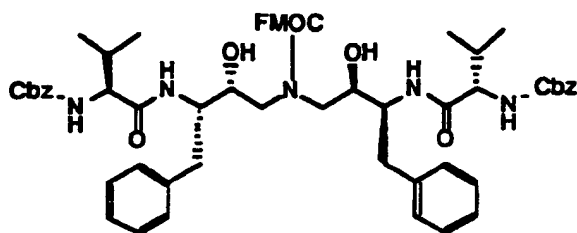


Compound 39 was converted to the title Compound 40 by a procedure analogous to the one used for the synthesis of Compound 32. R<sub>f</sub> = 0.56 (20:6:80, MeOH:NH<sub>4</sub>OH:CHCl<sub>3</sub>).

### Example 41

Preparation of [S-(1S\*,2R\*)]-N,N'-[[[(9H-Fluoren-9-ylmethoxy)carbonyl]imino]bis-[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis[N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide] (Compound 41)

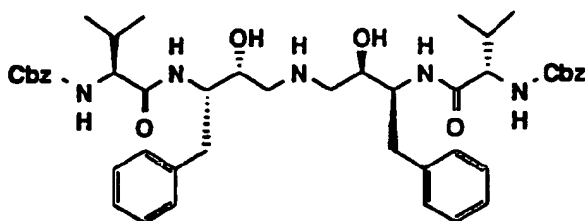




Compound 40 was coupled with Cbz-L-valine by a procedure analogous to the one used for the synthesis of Compound 33 (DMF was used) to give the title Compound 41.  $R_f = 0.69$  (1:9, MeOH:CH<sub>2</sub>Cl<sub>2</sub>).

#### Example 42

Preparation of [1S-(1R\*,2S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis[N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide] (Compound 42)



To a mixture of Compound 41 (110 mg, 0.107 mmol) in DMF (4 mL) at RT was added piperidine (0.20 mL). After 50 min, the reaction mixture was diluted with H<sub>2</sub>O and the resulting solid was collected by filtration and washed with H<sub>2</sub>O and hexanes. The resulting residue was purified by flash chromatography (silica gel, 2 by 13 cm), eluting with MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub> (7:0.7:92.3, 8:0.8:91.2, and then 9:0.9:90.1) to give the title Compound 42 (65 mg, 75% yield) as a colorless solid.

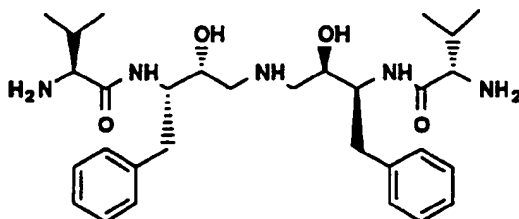
m.p. dec. 217-221°C;  $[\alpha]_D^{25} = -14.14^\circ$  (c 0.21, DMSO); MS: 810 (M+H).

Anal. Calc. for C<sub>48</sub>H<sub>69</sub>N<sub>6</sub>O<sub>8</sub> · 0.56 H<sub>2</sub>O:

	C, 67.37;	H, 7.39;	N, 8.54
Found:	C, 67.43;	H, 7.17;	N, 8.48

#### Example 43

Preparation of [S-(1S\*,2R\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis-L-valinamide (Compound 43)



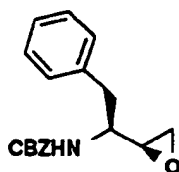
A mixture of Compound 42 (65 mg, 81 μmol) and Pd(OH)<sub>2</sub> (23 mg) in aqueous HOAc (3 mL, 90%) at RT

was stirred under an  $H_2$  for 2.5 h, filtered through Celite, washing the filter pad with aqueous HOAc, and the volatiles were removed *in vacuo*. The resulting oily-residue was co-evaporated with dry  $Et_2O$  to give a colorless solid (60 mg). This residue was dissolved in  $H_2O$ , basified to pH 9-10 with saturated aqueous  $K_2CO_3$  and purified by CHP-20P resin chromatography, eluting with  $H_2O$ , then  $CH_3CN:NH_4OH:H_2O$  and the column flushed with  $MeOH:NH_4OH:H_2O$  to give the title Compound 43 (29 mg, ~62% yield) as a slightly colored solid. m.p. 115-116°C. MS: 542 (M+H).

#### Example 44

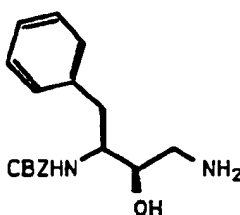
Preparation of [R-(R\*,S\*)]-Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propandiyl]]biscarbamic acid, bis(phenylmethyl) ester (Compound 44c)

##### (a) Compound 44a



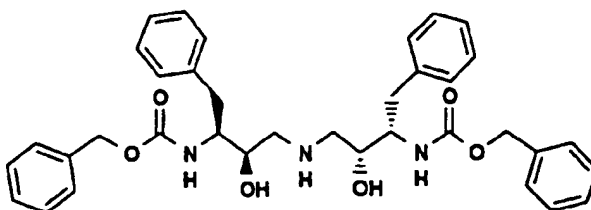
Compound 44a was prepared by procedures analogous to those used for the synthesis of Compound 1b(i), in which N-Cbz-L-phenylalanine was employed in place of N-Boc-L-phenylalanine.

##### (b) Compound 44b



Compound 44a was converted into Compound 44b by a procedure analogous to the one used for the synthesis of Compound 16b except that the reaction was done in MeOH saturated with  $NH_3$  at 55°C for 40 h in a sealed bottle.

##### (c) Compound 44c



Compounds 44a and 44b (1 equivalent of each) were reacted by a procedure analogous to that used for the preparation of Compound 4b to give the title Compound 44c (white solid).

mp 167-171°C;  $[\alpha]_D = -27.7^\circ$  (c 0.13, AcOH).

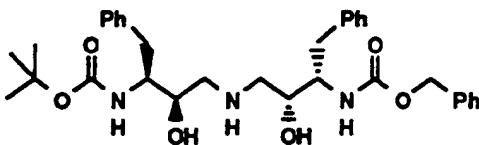
Mass Spec. 612 (M + H).

Analysis Calc. for  $C_{36}H_{41}N_3O_6 \cdot 1.43H_2O$ :

	C, 67.82;	H, 6.93;	N, 6.59;
Found:	C, 68.12;	H, 6.56;	N, 6.29.

**Example 45**

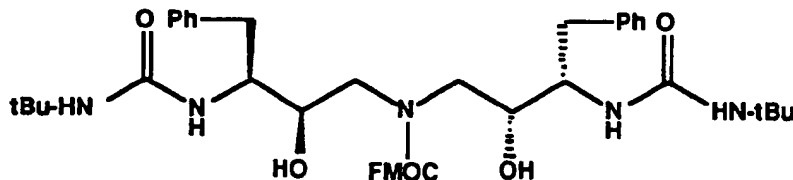
**Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl phenylmethyl ester (Compound 45)]**



To a solution of lithium perchlorate (16.4 g, 0.155 mol) in 500 ml  $CH_3CN$  was added Compound 16b (43.5 g, 0.155 mol) as a solid followed by Compound 44a (41.2 g, 0.139 mole) in 150 ml  $CH_3CN$ . The resulting mixture was stirred at 30°C for 2 h and at 40°C for 30 h at which point it was cooled to RT then added to 1.5L of  $H_2O$ . The resulting precipitate was filtered and triturated with i-PrOH followed by 1:1 EtOAc:i-PrOH (2X) to give 42.1 g (52%) of Compound 45 as a white solid.  
m.p. 169-173°;  $[\alpha]_D = -13.9^\circ$  (c 1.3, MeOH).

**Example 46**

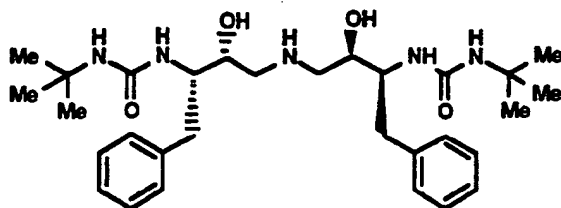
**Preparation of [R-(R\*,S\*)]-N,N'-[[(9H-Fluoren-9-ylmethoxy)carbonyl]iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis[N'-(1,1-dimethylethyl)urea] (Compound 46)]**



To a suspension of Compound 40 (59 mg, 92  $\mu$ mol) in  $CH_2Cl_2$  (1 mL) was added  $Et_3N$  (40  $\mu$ L) followed by tert-butylisocyanate (20 mg, 0.201 mmol). After 3 h, a second portion of tert-butylisocyanate (4.3 mg, 0.044 mmol) was added and after a further 2 h the volatiles were removed *in vacuo* to leave a colorless solid. The residue was purified by flash chromatography (silica gel, 1 by 14 cm), eluting with 0.5, 3, and then 4% MeOH: $CH_2Cl_2$  to give the title Compound 46 (55 mg, 79% yield) as a colorless solid.  $R_f = 0.56$  (10:90, MeOH: $CH_2Cl_2$ ) (PMA); Mass Spec.(FAB): 764 (M+H).

**Example 47**

**Preparation of [R-(R\*,S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis[N'-(1,1-dimethylethyl)urea] (Compound 47)]**



Compound 46 was converted to the title Compound 47 by a procedure analogous to the one used for the synthesis of Compound 42.

m.p. 108-110°C;  $[\alpha]_D^{25} = +1.93^\circ$  (c 0.19, MeOH).

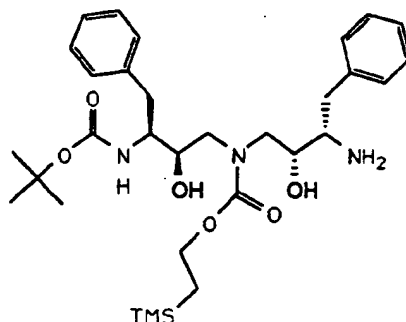
MS: (CI): 542 (M+H).

Anal. Calc. for  $C_{30}H_{47}N_5O_4 \cdot 0.84 H_2O$ :

	C, 64.70;	H, 8.81;	N, 12.58
Found:	C, 64.85;	H, 8.71;	N, 12.43

#### Example 48

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[(3-Amino-2-hydroxy-4-phenylbutyl)-[2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 48)

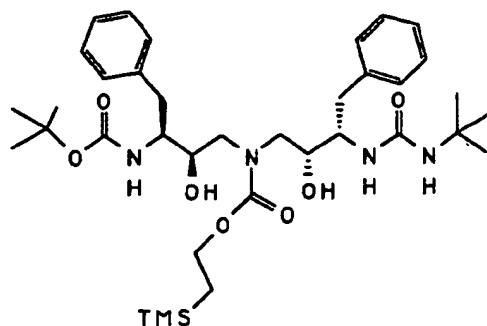


Compound 45 was converted to the title Compound 48 by a two-step procedure analogous to the conversion of Compound 17b to Compound 19 (MeOH was used in removing the carbobenzyloxy group).

$^1H$  NMR ( $CD_3OD$ ):  $\delta$  0.05 (s, 9H), 1.03 (m, 2H), 1.30 (s, 9H), 2.60 (m, 2H), 3.00 (m, 3H), 3.21 (m, 1H), 3.45-3.82 (m's, 6H), 4.12 (m, 2H), 7.11-7.28 (m, 10H).

#### Example 49

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethyl]amino]carbonyl]amino]-2-hydroxy-4-phenylbutyl][2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 49)

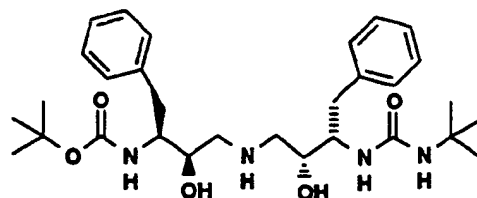


Compound 48 was converted to the title Compound 49 by a procedure analogous to that used for the synthesis of Compound 46.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 0.05 (s, 9H), 0.98 (m, 2H), 1.20 (s, 9H), 1.27 (s, 9H), 2.65 (m, 2H), 3.05 (m, 2H), 3.25 (m, 2H), 3.60-3.85 (m's, 6H), 4.15 (m, 2H), 7.10-7.30 (m, 10H).

#### Example 50

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethyl)amino]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 50)



Compound 49 was deprotected by a procedure analogous to the one used for the synthesis of Compound 21 to give the title Compound 50.

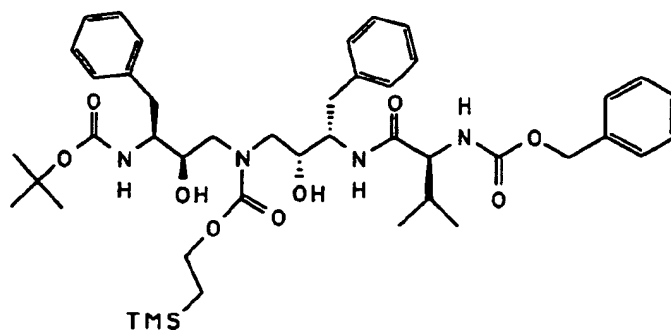
mp 110-112°C.; [α]<sub>D</sub> = -3.5° (c 0.2, MeOH).

Mass Spec.: 543 (M + H).

Analysis calc. for C <sub>30</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> ·1.39H <sub>2</sub> O:			
	C, 63.46;	H, 8.66;	N, 9.87;
Found:	C, 63.78;	H, 8.21;	N, 9.55.

#### Example 51

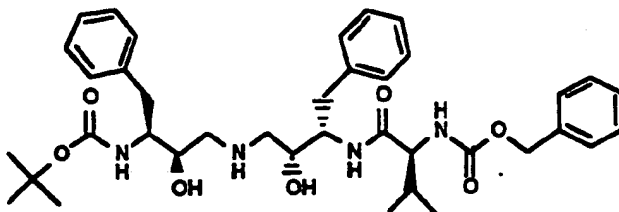
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]]2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 51)



EDC (44 mg; 0.23 mmol) was added to a solution of Cbz-valine (54 mg; 0.23 mmol) and HOBt (35 mg; 0.23 mmol) in 1 ml of DMF at 0°C. After stirring at 0°C for 1 h, Compound 48 (124 mg; 0.21 mmol) was added, followed by N-methylmorpholine (28 ml; 0.25 mmol). The reaction mixture was allowed to warm to RT and stir for 20 h, after which time it was partitioned between EtOAc (30 ml) and H<sub>2</sub>O (30 ml). The organic layer was washed with saturated aqueous KHSO<sub>4</sub> (2X), H<sub>2</sub>O, 1N NaOH (2X), H<sub>2</sub>O and brine. The organic layer was dried (MgSO<sub>4</sub>), concentrated, and the resulting residue purified by silica gel column chromatography (2.5 x 12 cm), eluting with 1:1 EtOAc:hexane to afford 137 mg (80%) of Compound 51 as a white foam. Mass Spec.: 821 (M + H).

#### Example 52

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 52)



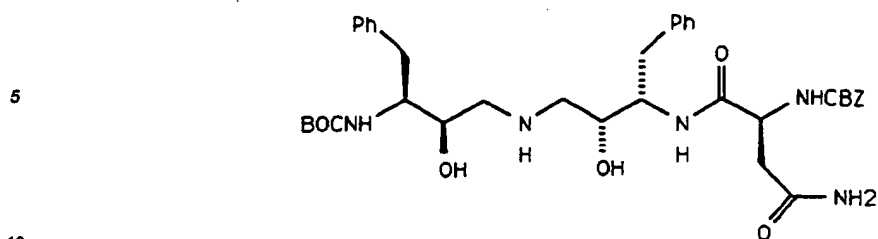
Compound 51 was deprotected by a procedure analogous to the one used for the synthesis of Compound 21 to give the title Compound 52 (white solid). mp 202-204°C; [α]<sub>D</sub> = -31.4° (c 0.07, AcOH). Mass Spec.: 677 (M + H).

Analysis calc. for C<sub>38</sub>H<sub>62</sub>N<sub>4</sub>O<sub>7</sub>·0.22H<sub>2</sub>O:

	C, 67.04;	H, 7.76;	N, 8.23;
Found:	C, 67.01;	H, 7.79;	N, 8.26.

#### Example 53

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)-carbonyl]-L-aspartamide (Compound 53)



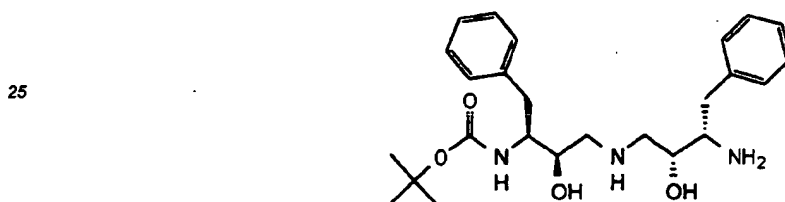
The title Compound 53 was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that Cbz-asparagine was used.

mp 182 - 185°C;  $[\alpha]_D = -26.7^\circ$  (c 0.4, AcOH)

High Resolution mass spec. (M+H): 692.3665; calc'd for  $C_{37}H_{50}N_5O_8$ : 692.3659.

#### Example 54

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]-3-[(3-Amino-2-hydroxy-4-phenylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 54)

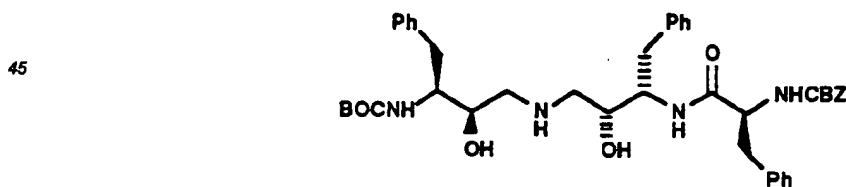


A suspension of 1.0 g (1.73 mmol) of Compound 45 in 12 ml of EtOH and 6 ml of cyclohexene along with 0.1 g of Pd(OH)<sub>2</sub>/C was stirred at reflux (oil bath temp. = 85°) for 1 h. The reaction mixture was cooled to RT and filtered through a plug of Celite on a nylon-66 filter and the filtrate evaporated to dryness to give 0.705 g (92%) of a white solid containing the title Compound 54.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.30 (s, 9H), [1.18 - rotamer], 2.45 - 2.64 (m, 2H), 2.65 - 2.84 (m, 4H), 2.93 - 3.15 (m, 3H), 3.56 - 3.73 (m, 3H), 7.10 - 7.36 (m, 10H).

#### Example 55

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-(hydroxy-1-(phenylmethyl)propyl)-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-phenylalaninamide (Compound 55)



EDC (38.4 mg, 0.20 mmol) was added to a solution of Cbz-phenylalanine (57.0 mg, 0.19 mmol) and HOBT (33.0 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.8 mL) at 0°C under argon. After stirring at 0°C for 1 hr, Compound 54 (77.0 mg, 0.17 mmol) was added in dry DMF (1.0 mL). The reaction mixture was allowed to warm to RT and stirred overnight. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and washed with saturated NaHCO<sub>3</sub> solution (15 mL), H<sub>2</sub>O (15 mL), and brine (15 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude material was purified by flash chromatography (silica gel; 1.5 x 15 cm) eluting with CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH (gradient from 98.9:1:0.1 to 89:9:1) to give 76 mg of the title Compound 55 (62%).

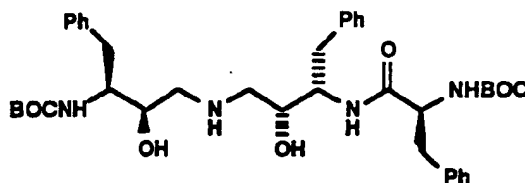
mp 185 - 188°C;  $[\alpha]_D = -27.8^\circ$  (c 0.2, MeOH)

High Resolution mass spec. (M + H)<sup>+</sup>: 725.3906;

Calc'd for  $C_{42}H_{53}N_4O_7$ : 725.3914.

### Example 56

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[(1,1-Dimethylethoxy)carbonyl]-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)-propyl]-L-phenylalaninamide (Compound 56)



The title Compound 56 was prepared from Compound 54 and Boc-phenylalanine by a procedure analogous to that used for the synthesis of Compound 55.

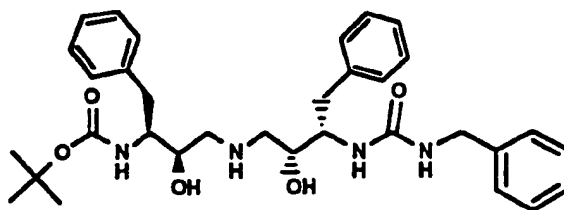
mp 179 - 182 °C;  $[\alpha]_D = -14.4^\circ$  (c 0.6, MeOH)

Mass Spec.: (M + H) = 691

Analysis calculated for $C_{39}H_{54}N_4O_7 \cdot 0.47 H_2O$ :			
	C, 66.90	H, 7.92	N, 8.01
Found:	C, 67.00	H, 7.64	N, 7.99

### Example 57

Preparation of [1R\*,2S\*(2S\*,3R\*)]-[2-Hydroxy-3-[[2-hydroxy-4-phenyl-3-[[[(phenylmethyl)amino]carbonyl]amino]butyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 57)



The title Compound 57 was prepared from Compound 48 by a two-step procedure analogous to the one used for the synthesis of Compound 50 except that benzylisocyanate was used in place of tert-butylisocyanate.

mp 161 - 165 °C;  $[\alpha]_D = -11.9^\circ$  (c 0.5, MeOH).

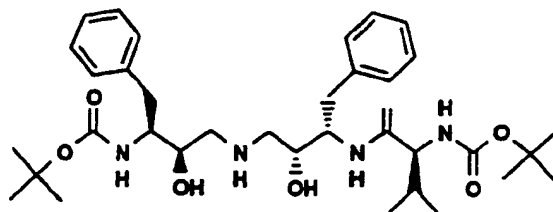
Mass Spec. (M + H) 577

Analysis calculated for $C_{33}H_{44}N_4O_5 \cdot 0.40 H_2O$			
	C, 67.88;	H, 7.73;	N, 9.60;
Found:	C, 67.90;	H, 7.59;	N, 9.58.

### Example 58

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(1,1-dimethylethoxy)carbonyl]-L-valinamide (Compound 58)





The title Compound 58 (white solid) was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that Boc-valine was used.

mp 182-187°C.;  $[\alpha]_D = -11.7^\circ$  (c 0.06, AcOH).

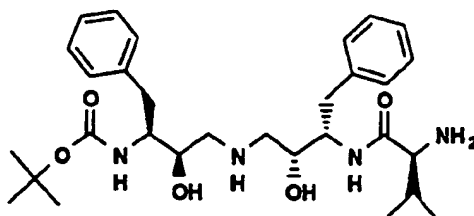
Mass Spec.: 642 (M + H).

Analysis calc. for  $C_{35}H_{54}N_4O_7 \cdot 0.26H_2O$ :

	C, 64.93;	H, 8.49;	N, 8.65;
Found:	C, 64.80;	H, 8.35;	N, 8.78.

#### Example 59

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl-L-valinamide (Compound 59)



The title Compound 59 (white solid) was prepared from Compound 52 by a procedure analogous to the one used for the preparation of Compound 43.

mp 131-137°C;  $[\alpha]_D = +6.0^\circ$  (c 0.2, MeOH).

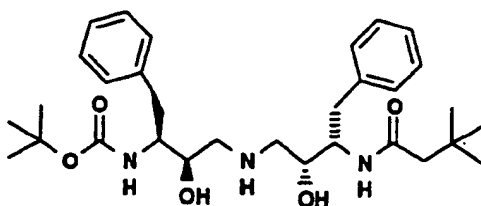
Mass Spec.: 543 (M + H).

Analysis calc. for  $C_{30}H_{46}N_4O_5 \cdot 1.14H_2O$ :

C, 63.97;	H, 8.64;	N, 9.95;
Found: C, 63.96;	H, 8.39;	N, 9.96.

#### Example 60

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(3,3-Dimethyl-1-oxybutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 60)



The title Compound 60 was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that tert-butylacetic acid was used in place of Cbz-valine ( $\text{CH}_2\text{Cl}_2$  replaced DMF and no N-methyl morpholine was used in the EDC coupling).  
p 153-156°C;  $[\alpha]_D^{20} = -3.3^\circ$  (c 0.1, MeOH).

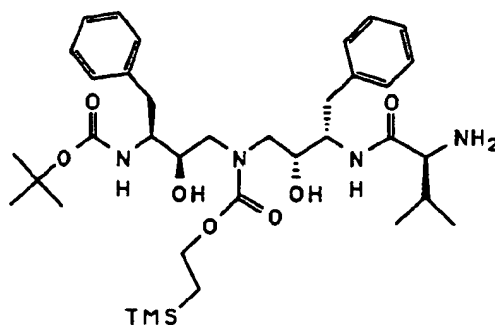
Mass Spec.: 542 (M + H).

Analysis calc. for  $\text{C}_{31}\text{H}_{47}\text{N}_3\text{O}_6 \cdot 0.54 \text{ H}_2\text{O}$ :

	C, 67.52;	H, 8.79;	N, 7.62;
Found:	C, 67.88;	H, 8.80;	N, 7.26.

#### Example 61

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]]-[2-(trimethylsilyl)ethoxy]-carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 61)

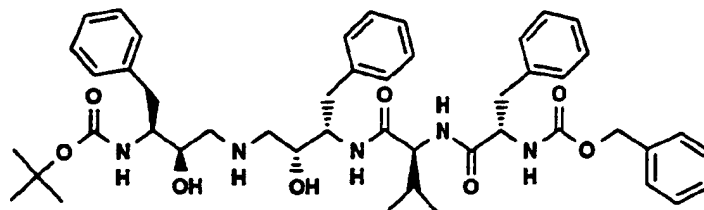


A suspension of Compound 51 (385 mg; 0.47 mmol) and 110 mg of  $\text{Pd}(\text{OH})_2/\text{C}$  in 5 ml of MeOH was stirred at RT under a  $\text{H}_2$  atmosphere for 1.5 h. The reaction mixture was filtered through a Nylon-66, 0.45 micron filter to remove the catalyst and the filtrate was concentrated to dryness. The residue was chromatographed on a 2.5 x 20 cm silica gel column, using 5% MeOH/ $\text{CH}_2\text{Cl}_2$  as the mobile phase to afford 306 mg (95%) of the title Compound 61 as a white foam.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ;  $60^\circ\text{C}$ ):  $\delta$  0.02 (s, 9H), 0.56 (J = 7 Hz, 3H), 0.74 (d, J = 7 Hz, 3H), 0.95 (t, J = 7.5, 9.5 Hz, 2H), 1.25 (s, 9H), 1.48 (brs, 2H), 1.80 (m, 1H), 2.62 (m, 2H), 2.87 (d, J = 4.5 Hz, 1H), 2.97 (m, 2H), 3.59 (m, 3H), 3.69 (m, 2H), 3.94 (m, 1H), 4.06 (dd, J = 7.5, 14.5 Hz, 2H), 4.87 (m, 1H), 4.97 (m, 1H), 6.37 (brs, 1H), 7.14 (m, 2H), 7.20 (m, 10H), 7.57 (d, J = 9 Hz, 1H).

#### Example 62

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethyl)carbonyl]-L-phenylalanyl]-L-valinamide (Compound 62)



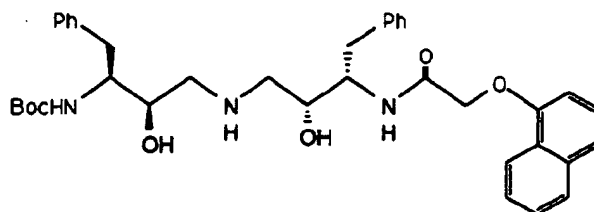
The title Compound 62 (white solid) was prepared from Compound 61 and Cbz-phenylalanine by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.  
mp 215-218°C.;  $[\alpha]_D = -20.7^\circ$  (C 0.15, AcOH).  
Mass Spec.: (M+H = 824).

Analysis calc. for  $C_{47}H_{61}N_5O_8 \cdot 0.90 H_2O$ :

	C, 67.19;	H, 7.53;	N, 8.33;
Found:	C, 67.25;	H, 7.25;	N, 8.27.

#### Example 63

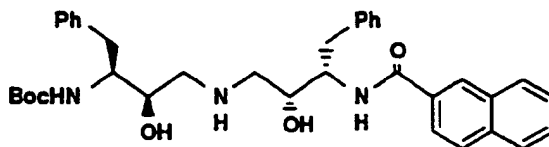
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(1-naphthalenyloxy)acetyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 63)



The title Compound 63 was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that (1-naphthoxy)acetic acid was used.  
m.p. 182-185°C.;  $[\alpha]_D = -58.5^\circ$  (c = 0.19, MeOH).  
High Resolution Mass Spec: (M+H = 628.3397;  $C_{37}H_{46}N_3O_6$ ; 1.7 ppm error).

#### Example 64

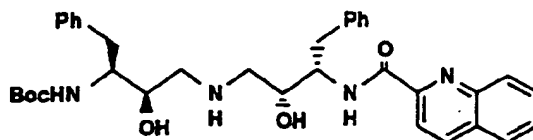
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(2-naphthalenylcarbonyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 64)



The title Compound 64 was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that 2-naphthoic acid was used.  
m.p. 188 - 192°C.;  $[\alpha]_D = -64.1^\circ$  (c = 0.19, MeOH).  
High Resolution Mass Spec: (M + H = 598.3292;  $C_{38}H_{44}N_3O_5$ ; 1.8 ppm error).

## Example 65

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-4-phenyl-3-[(2-quinolinylcarbonyl)amino]butyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 65)



The title Compound 65 was prepared from Compound 48 by a two-step procedure analogous to that used for the synthesis of Compound 52 except that quinaldic acid was used.

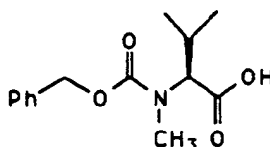
m.p. 192-196°C;  $[\alpha]_D = -67.2^\circ$  (c = 3.75, MeOH).

High Resolution Mass Spec: (M+H = 599.3257;  $C_{35}H_{43}N_4O_5$ ; 4 ppm error).

## Example 66

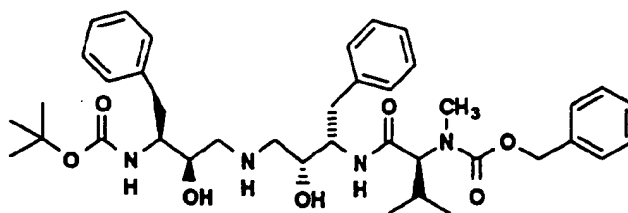
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-methyl-N<sup>2</sup>[(phenylmethoxy)carbonyl]-L-valinamide (Compound 66b)

## (a) Compound 66a



To a solution of N-Cbz-L-valine (2.51 g, 10.0 mmol) and  $CH_3I$  (5.0 mL, 80.0 mmol) in dry THF (30 mL) cooled at 0°C was added NaH (0.90 g of 80% dispersion in mineral oil, 30.0 mmol) in portions. After the addition, the suspension was stirred at RT for 12 h at which time additional  $CH_3I$  (1.5 mL, 24.0 mmol) was added, followed by 0.25 g of NaH (80%, 8.3 mmol). After the suspension was stirred for an additional 24 h, EtOAc (50 mL) was added. The mixture was stirred for 30 min at RT, and then cooled down to 0°C.  $H_2O$  was added dropwise to destroy NaH. The solvents were removed *in vacuo*, the oily residual partitioned between  $H_2O$  and  $Et_2O$ , and the aqueous layer extracted with  $Et_2O$ . The combined  $Et_2O$  solution was extracted with 40 % aqueous  $NaHCO_3$  and the combined aqueous phase acidified with 4 N HCl to pH 2 and extracted with EtOAc. The EtOAc extracts were washed with  $H_2O$ , 5% aqueous  $Na_2S_2O_3$ ,  $H_2O$ , dried over  $MgSO_4$  and evaporated *in vacuo* to dryness to give a pale yellow oil, which was crystallized from  $Et_2O$  and pentane to afford white crystalline Compound 66a. (2.97g, 97%). mp. 66-67°C

## (b) Compound 66b

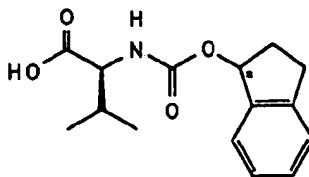


The title Compound 66b was prepared from Compounds 54 and 66a by a procedure analogous to that used for the synthesis of Compound 55 (1 eq. of N-methylmorpholine was added along with Compound 54). mp 67-70°C;  $[\alpha]_D = -59.3^\circ$  (c 0.8, MeOH).

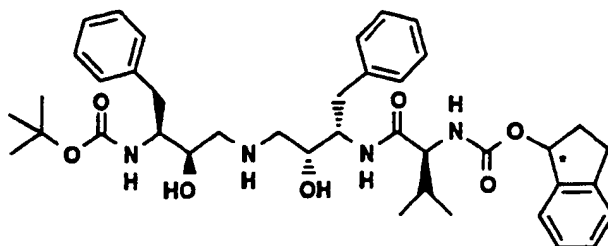
Analysis calc. for $C_{39}H_{64}N_4O_7 \cdot 1.15 H_2O$ :			
	C, 65.84;	H, 7.97;	N, 7.87;
Found:	C, 65.94;	H, 7.62;	N, 7.77.

Preparation of [S-(1R\*,2S\*(2S\*,3R\*))]-N<sup>2</sup>-[[2,3-Dihydro-1H-inden-1-yl]oxy]carbonyl-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 67c)

**(b) Compound 67b**



A suspension of 117 mg (1.00 mmol) of L-valine in 1 mL of 1.0N NaOH was stirred for 30 min and then treated with a solution of 299 mg (1.00 mmol) of Compound 67a in 2 mL of t-butanol and 1 mL of dioxane. The reaction mixture was stirred at RT overnight. 0.2 mL of Et<sub>3</sub>N was added to the mixture to increase the rate of the reaction and stirring was continued for 48 h. The reaction mixture was diluted with 50 mL of EtOAc, and washed with 5% KHSO<sub>4</sub> (2x25 mL), and saturated NaCl (25 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to provide 355 mg of crude acid. Flash chromatography on silica gel, eluting with 50% EtOAc-hexane and then 50% EtOAc-hexane with 0.5% HOAc, afforded 209 mg (75%) of Compound 67b, as a white solid.

(c) Compound 67c

The title Compound 67c was prepared as a mixture of diastereomers from Compound 54 and Compound 67b by a procedure analogous to that used for the synthesis of Compound 55.

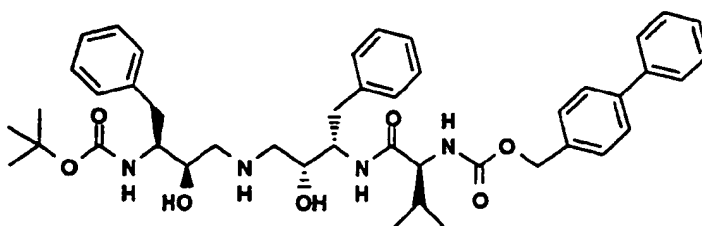
mp 202-206°C;  $[\alpha]_D^{20} = -15^\circ$  (c=0.071, CH<sub>3</sub>OH)

Mass Spec. 703 (M+H)<sup>+</sup>

Elemental Analysis (%) C <sub>40</sub> H <sub>54</sub> N <sub>4</sub> O <sub>7</sub>		
	Calc.	Found
C	68.35	68.13
H	7.74	7.84
N	7.97	7.70

### Example 68

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N<sup>2</sup>-[[[1,1'-Biphenyl]-4-ylmethoxy]carbonyl-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 68)



The title Compound 68 was prepared from Compound 54 by a three-step procedure analogous to that used for the synthesis of Compound 67c except that 4-biphenylmethanol was used in the first step and 1.1 eq. of Et<sub>3</sub>N (no t-BuOH) was used in the second step.

mp 208-211°C;  $[\alpha]_D^{20} = -19^\circ$  (c=0.077, CH<sub>3</sub>OH)

Mass Spec. 753 (M+H)<sup>+</sup>

Elemental Analysis (%)

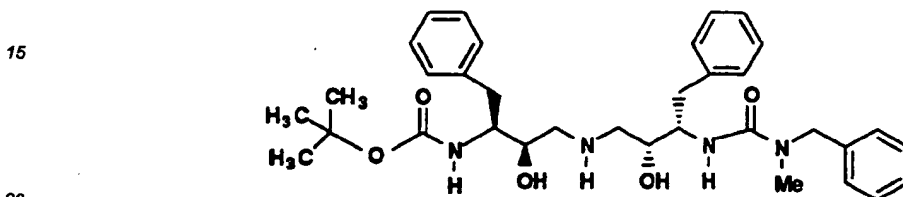
C<sub>44</sub>H<sub>56</sub>N<sub>4</sub>O<sub>7</sub>

Calc. Found

	C	70.19	69.91
5	H	7.50	7.48
	N	7.44	7.23

### Example 69

10 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-2-Hydroxy-3-[[[2-hydroxy-3-[[[methyl(phenylmethyl)amino]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 69)



The title Compound 69 (white solid) was prepared from Compound 48 and N-benzyl-N-methyl carbamoyl chloride (*Bull. Chem. Soc. Jpn.*, 50, 1872 (1977)) by a two-step procedure analogous to that used for the synthesis of Compound 50.

25 mp 97-99°C;  $[\alpha]_D^{25} = -18.8^\circ$  (c 0.5, CH<sub>3</sub>OH).

Mass Spec. (FAB) (M + H)<sup>+</sup> = 591

Analysis calc. for C <sub>34</sub> H <sub>46</sub> N <sub>4</sub> O <sub>5</sub> ·0.89H <sub>2</sub> O:			
30 Calculated	C, 67.31;	H, 7.94;	N, 9.23;
Found:	C, 67.42;	H, 7.83;	N, 9.12.

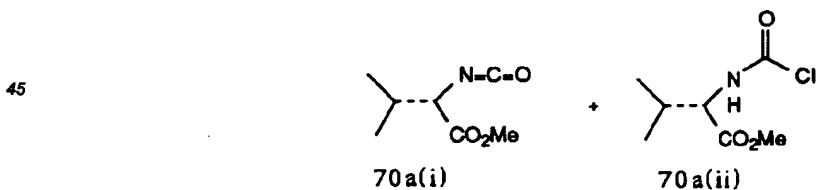
### Example 70

35

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(2-pyridinylmethoxy)carbonyl]-L-valinamide (Compound 70d)

40

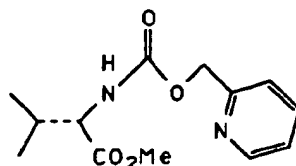
(a) Compounds 70a(i) and 70a(ii)



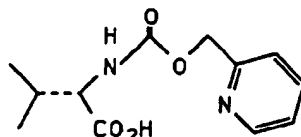
50

To a solution of L-valine methyl ester hydrochloride (2.5 g; 14.9 mmol) in 14.9 mL of dry dioxane was added trichloromethyl chloroformate (1.5 g; 7.6 mmol) at RT. The mixture was heated at 60°C for 3.5 h. The clear solution was cooled to RT and concentrated *in vacuo* to give an oil, which was azeotroped from dry toluene (2x10 mL) to give Compounds 70a(i) and 70a(ii).

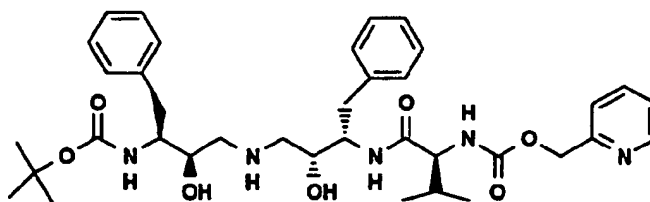
55

(b) Compound 70b

To a solution of the crude Compounds 70a(i) and 70a(ii) (2.3 g; 14.9 mmol) in 48 mL of dry toluene was added 1.6 g (14.9 mmol) of 2-pyridylcarbinol. The mixture was heated to reflux for 12 h and then concentrated *in vacuo* to a residue. Purification by flash chromatography (silica gel; 25% acetone-hexane) afforded 1.08 g (27% over two steps) of Compound 70b.

(c) Compound 70c

To a solution of Compound 70b (223 mg; 0.83 mmol) in 3.3 mL of dry dioxane was added 3.0 mL of 0.5M LiOH. After 12 h at RT, the reaction mixture was acidified with 1 N HCl (1.5 ml) and then evaporated to dryness. Further drying over P<sub>2</sub>O<sub>5</sub> under vacuum at RT gave 300 mg (~100%) of a brown residue containing Compound 70c.

(d) Compound 70d

The title Compound 70d was prepared from Compounds 54 and crude 70c by a procedure analogous to that used for the synthesis of Compound 55 (1 eq. of N-methylmorpholine was used).  
m.p. 175 - 178°C;  $[\alpha]_D^{25} = -16.0^\circ$  (c 0.13, MeOH).

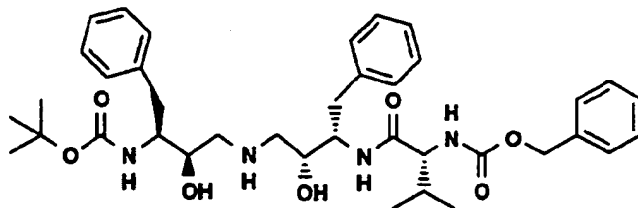
Mass spec. (M+H) 678

Elemental Analysis (%) C <sub>37</sub> H <sub>51</sub> N <sub>5</sub> O <sub>7</sub> ·2.90 H <sub>2</sub> O		
	Calc.	Found
C	60.87	60.84
H	7.54	7.30
N	9.59	9.57



## Exempl 71

Preparation of [R-[1S\*,2R\*(2R\*,3S\*)]]-N-[3-[[[3-[(1,1-Dimethyl thoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-phenylmethyl]propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-D-valinamid (Compound 71)



The title Compound 71 was prepared from Compounds 54 and N-Cbz-D-valine by a procedure analogous to that used for the synthesis of Compound 55.

mp 185-187°C.;  $[\alpha]_D^{25} = +16.25^\circ$  (c 0.16, MeOH).

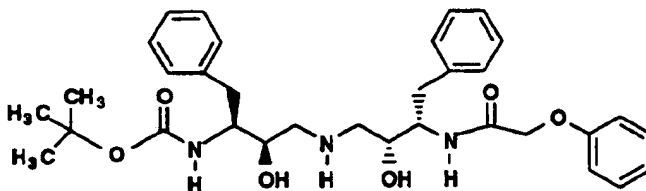
Mass Spec. FAB  $[M+H]^+$ : 677.

Analysis calc. for  $C_{38}H_{52}N_4O_7 \cdot 1.63 H_2O$ :

	C, 64.63;	H, 7.89;	N, 7.93;
Found:	C, 64.63;	H, 7.70;	N, 8.12.

## Example 72

Preparation of 1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(phenoxycetyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 72)



The title Compound 72 (white solid) was prepared from Compounds 54 and phenoxycetic acid by a procedure analogous to that used for the synthesis of Compound 55 (1 eq. of N-methylmorpholine was used).

mp 162-165°C.;  $[\alpha]_D^{25} = -17.6^\circ$  (c 0.5, CH<sub>3</sub>OH).

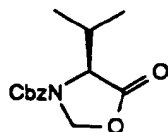
Mass Spec.(FAB) (M + H)<sup>+</sup> = 578

Analysis calc. for  $C_{33}H_{43}N_3O_6$ :

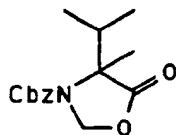
Calculated	C, 68.61;	H, 7.50;	N, 7.27;
Found:	C, 68.59;	H, 7.58;	N, 7.33.

## Example 73

Preparation of [(S,R)-3-[[[(R,S)-3-[[2-[(Phenylmethoxy)carbonyl]amino]-2,3-dimethyl-1-oxybutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 73d)

(a) Compound 73a

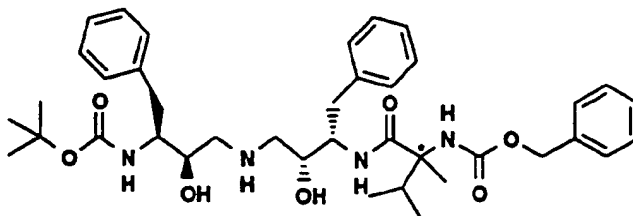
A suspension of N-Cbz-L-Valine (2.51 g, 10.0 mmol), paraformaldehyde (2.0 g) and p-toluenesulfonic acid (0.2 g) in 200 mL of toluene was heated to reflux for 2 h. After being cooled down to RT, the reaction mixture was washed with saturated NaHCO<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. The filtrate was concentrated *in vacuo* to afford 2.32 g (88%) of Compound 73a as a light yellow solid.

(b) Compound 73b

To a solution of crude Compound 73a (0.76 g; 2.88 mmol) in 10 ml of dry THF cooled at -78°C was added 6.62 ml (3.31 mmol) of KN(TMS)<sub>2</sub> (0.5 M solution in toluene) dropwise over 15 min. The reaction mixture was stirred at the same temperature for 15 min, then CH<sub>3</sub>I (0.216 ml, 3.46 mmol) was added dropwise. The mixture was stirred at -78°C for 20 min, -20°C for 20 min, then at 0°C for 1 h. The reaction was quenched with 10 ml pH 7 buffer, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 ml). The combined organics were washed with H<sub>2</sub>O, brine and dried over MgSO<sub>4</sub>. The filtrate was concentrated to dryness and the oily residue purified by flash chromatography (silica gel), using 20% EtOAc/hexane as the mobile phase to afford 0.487 g (61%) of Compound 73b as a colorless oil.

(c) Compound 73c

A solution of Compound 73b (0.46 g, 1.66 mmol) in 5 ml of MeOH and 5 ml of 1N NaOH was heated at 55°C for 30 min. After removal of MeOH, the aqueous phase was acidified to pH 1-2 with 1N HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 ml). The combined CH<sub>2</sub>Cl<sub>2</sub> phase was washed with water, brine and dried over MgSO<sub>4</sub> to give after concentrating *in vacuo* 0.44 g (100%) of Compound 73c as a colorless oil.

(d) Compound 73d

Th titl Compound 73d was prepared as a 1:1 mixture of diastereomers from Compounds 54 and 73c by a procedure analogous to that used for the synthesis of Compound 55.  
mp 66-68°C; [α]<sub>D</sub><sup>20</sup> = -5.6° (c 0.25, MeOH).  
Mass Spec. [M+H]<sup>+</sup>: 691.

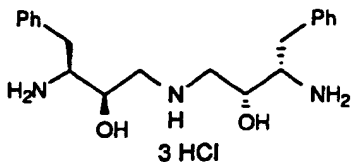
Analysis calc. for $C_{39}H_{64}N_4O_7 \cdot 0.46 H_2O$ :			
	C, 67.00;	H, 7.92;	N, 8.01;
Found:	C, 66.88;	H, 7.88;	N, 8.13.

	C, 67.00;	H, 7.92;	N, 8.01;
Found:	C, 66.88;	H, 7.88;	N, 8.13.

The diastereomers (at position indicated by an asterisk) were then separated by HPLC.

#### Example 74

Preparation of [(R-(R\*,S\*))]-1,1'-Iminobis(3-amino-4-phenyl-2-butanol), trihydrochloride (Compound 74)

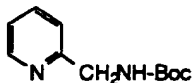


The title Compound 74 was prepared from Compound 2 by a procedure analogous to that used for the synthesis of Compound 32.  $R_f = 0.054$  (20:2:78 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>).

#### Example 75

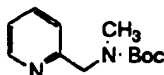
Preparation of [S-(1R\*,2S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis[N<sup>2</sup>-[[methyl(2-pyridinylmethyl)amino]carbonyl]-L-valinamide (Compound 75f)]

##### (a) Compound 75a



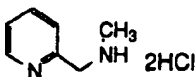
To a solution of di-*tert*-butyldicarbonate (63 g, 0.29 mole) in 600 ml of CH<sub>2</sub>Cl<sub>2</sub> at 0°C was added a solution of 2-(aminomethyl)pyridine (31.36 g, 0.29 mole) in 150 ml of CH<sub>2</sub>Cl<sub>2</sub> in a dropwise manner. After the addition was complete the mixture was allowed to slowly warm to RT and stir overnight. The reaction was washed with H<sub>2</sub>O (3 x 800 ml), brine (800 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>) to give, after concentration, 58.6 g (97%) of Compound 75a as a pale yellow oil.

##### (b) Compound 75b



Compound 75a was converted to Compound 75b by a procedure analogous to that used for the synthesis of Compound 66a except that DMF was used in place of THF.

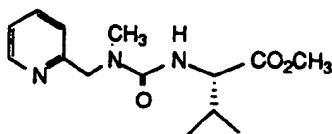
##### (c) Compound 75c



Compound 75b was converted to Compound 75c by a procedure analogous to that used for the synthesis

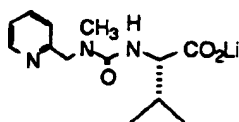
of Compound 32 except that the reaction was run at 40°C.

(d) Compound 75d



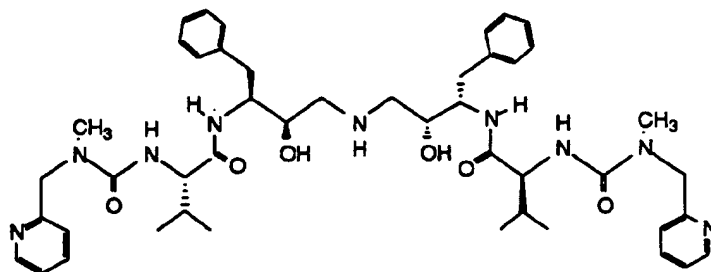
Compound 75c was converted to Compound 75d by a procedure analogous to that used for the synthesis of Compound 70b except that CH<sub>2</sub>Cl<sub>2</sub> replaced toluene and 2.5 eq. of N-methylmorpholine was added.

(e) Compound 75e



Compound 75d was converted to Compound 75e by a procedure analogous to that used for the synthesis of Compound 70c (the reaction was quenched with one equivalent of 1N HCl).

(f) Compound 75f



A mixture of Compound 74 (136 mg, 0.25 mmol), HOBT (84 mg, 0.55 mmol), and Compound 75e (148 mg, 0.55 mmol) in 0.6 ml of dry DMF was cooled to 0°C. EDCI (108 mg, 0.55 mmol) was added followed by 6 eq. of N-methylmorpholine (167 mg, 3.3 mmol). The mixture was stirred at 0°C for several hours and was then allowed to slowly warm to RT and stir overnight. The DMF was removed *in vacuo* and the residue was partitioned between saturated NaHCO<sub>3</sub> (10 ml) and EtOAc (15 ml). The EtOAc layer was washed with additional saturated NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub> and evaporated to give a crude yellow solid which purified on a 30 ml silica column (CC-7, pH6.8) eluting with 5% - 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.1% NH<sub>4</sub>OH to afford 86 mg (41%) of the title Compound 75f as a colorless solid.  
m.p. 178-182°C; [α]<sub>D</sub> = 22.4° (c, 0.25, MeOH)

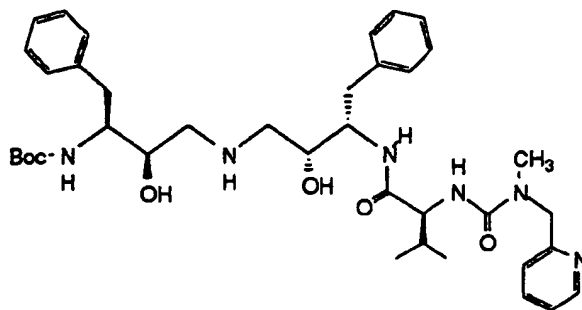
Analysis calc. for C<sub>46</sub>H<sub>63</sub>N<sub>9</sub>O<sub>8</sub> · 2.0 H<sub>2</sub>O:

	C, 63.21;	H, 7.73;	N, 14.42;
Found:	C, 63.51;	H, 7.52;	N, 14.12.

Example 76

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethyl thoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]-

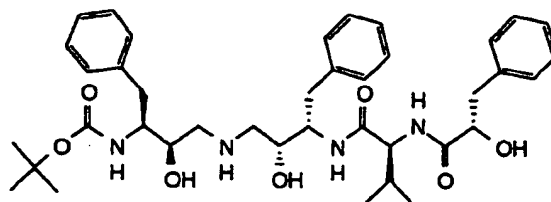
tyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[methyl(2-pyridinylmethyl)amino]carbonyl]-L-valinamide  
(Compound 76)



To a solution of Compound 54 (111 mg, 0.25 mmol), HOBT (42 mg, 0.275 mmol), and Compound 75e (74 mg, 0.275 mmol) in dry DMF (0.5 ml) at 0°C was added EDCI (53 mg, 0.275 mmol) followed immediately by N-methylmorpholine (91 µl, 83 mg, 0.825 mmol). The reaction was stirred several hours at 0°C and was then slowly warmed to RT and stirred overnight. The DMF was removed *in vacuo* and the resulting residue was partitioned between EtOAc (10 ml) and H<sub>2</sub>O (10 ml). The organic layer was washed with saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and concentrated to give a crude product which was purified on a 20 ml CC-7 silica column (Silica pH 6.8) eluting with 3% -> 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.1% NH<sub>4</sub>OH to afford a glasslike residue. Lyophilization from dioxane/H<sub>2</sub>O gave 48 mg (28%) of Compound 76 as a colorless solid. m.p. 184 - 188°C; [α]<sub>D</sub> = -16.4° (c = 0.2, MeOH) High Resolution Mass Spec. (FAB): C<sub>38</sub>H<sub>56</sub>N<sub>6</sub>O<sub>8</sub> = 691.4183; Δ = 0.35 ppm.

#### Example 77

Preparation of [S-[1R\*,2S\*,3R\*,N<sup>2</sup>R\*]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-hydroxy-1-oxo-3-phenylpropyl)-L-valinamide (Compound 77)

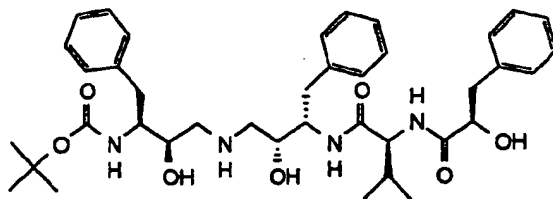


The title Compound 77 (white solid) was prepared from Compound 61 and L-phenyllactic acid by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52. mp 176-178°C; [α]<sub>D</sub> = -49.5° (C 0.16, MeOH). Mass Spec. FAB+ ion : (M+H) = 691.

Analysis calc. for C <sub>39</sub> H <sub>64</sub> N <sub>4</sub> O <sub>7</sub> ·0.61 H <sub>2</sub> O:			
	C, 66.75;	H, 7.93;	N, 7.98;
Found:	C, 66.81;	H, 7.69;	N, 7.92.

#### Exempl 78

Preparation of [S-[1R\*,2S\*[2S\*,3R\*,N<sup>2</sup>S\*]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-hydroxy-1-oxo-3-phenylpropyl)-L-valinamid

(Compound 78)

The title Compound 78 (white solid) was prepared from Compound 61 and D-phenyllactic acid by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

mp 188-194°C;  $[\alpha]_D = +7.6^\circ$  (c 0.17, MeOH).

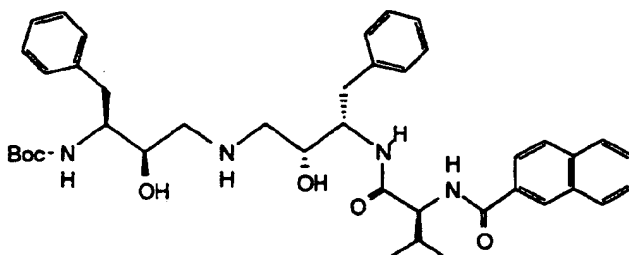
Mass Spec. FAB+ ion : (M+H) = 691.

Analysis calc. for  $C_{39}H_{54}N_4O_7 \cdot 1.42 H_2O$ :

	C, 65.38;	H, 8.00;	N, 7.82;
Found:	C, 65.26;	H, 7.84;	N, 7.94.

Example 79

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-naphthalenylcarbonyl)-L-valinamide (Compound 79)



The title Compound 79 was prepared from Compound 61 and 2-naphthoic acid by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

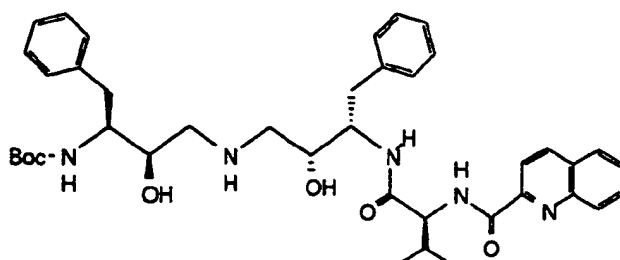
m.p. 192 - 196°C;  $[\alpha]_D = -12.6^\circ$  (c=0.18, MeOH)

Analysis: calc. for  $C_{41}H_{52}N_4O_6 \cdot 0.6 H_2O$ :

	C, 69.59;	H, 7.58;	N, 7.92;
Found:	C, 69.64;	H, 7.59;	N, 7.87.

Example 80

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-quinoliny carbonyl)-L-valinamide (Compound 80)



The title Compound 80 was prepared from Compound 61 and quinaldic acid by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

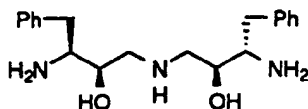
m.p. 192 - 194°C;  $[\alpha]_D = -14.5^\circ$  (c=0.24, MeOH)

Analysis calc. for  $C_{40}H_{51}N_5O_6 \cdot 0.64 H_2O$ :

	C, 67.73;	H, 7.43;	N, 9.87;
Found:	C, 67.98;	H, 7.56;	N, 9.62.

#### Example 81

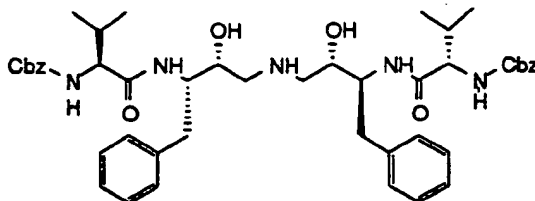
Preparation of [2R-[2R\*(2S\*,3S\*),3S\*]-1,1'-iminobis(3-amino-4-phenyl-2-butanol) hydrochloride (Compound 81)]



The title Compound 81 was prepared as a tri-HCl salt from Compound 5 by a procedure analogous to that used for the synthesis of Compound 32.  $R_f=0.07$  (15:1.5:84.5 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>).

#### Example 82

Preparation of [S-[1R\*,2R\*(2S\*,3R\*)]]-N-[2-Hydroxy-3-[[2-hydroxy-4-phenyl-3-[[N-(phenylmethoxy)carbonyl]-L-valyl]amino]butyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 82)]



The title Compound 82 was prepared from Compound 81 and Cbz-L-valine by a procedure analogous to that used for the synthesis of Compound 75f.

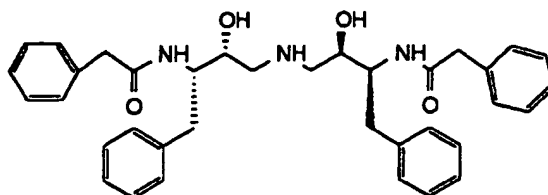
m.p. 216-219°C;  $[\alpha]_D^{25} = -34.8^\circ$  (c 0.28, DMSO).

Mass Spec.: (FAB): 810 (M+H).

Anal. Calc. for C <sub>46</sub> H <sub>59</sub> N <sub>5</sub> O <sub>8</sub> :			
	C, 68.21;	H, 7.34;	N, 8.65
Found:	C, 67.88;	H, 7.50;	N, 8.64

### Example 83

Preparation of [R-(R\*,S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bisbenzeneacetamide (Compound 83)



The title Compound 83 was prepared from Compound 74 and phenylacetic acid by a procedure analogous to that used for the synthesis of Compound 75f.

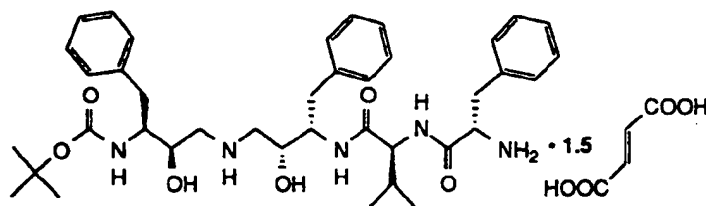
m.p. dec. 216-221°C;  $[\alpha]_D^{25} = +11.4^\circ$  (c 0.22, DMSO).

MS: (Cl/NH<sub>3</sub>): 580 (M+H).

Anal. Calc. for C <sub>36</sub> H <sub>44</sub> N <sub>3</sub> O <sub>4</sub> · 0.3 H <sub>2</sub> O:			
	C, 73.90;	H, 7.17;	N, 7.18
Found:	C, 73.88;	H, 7.03;	N, 7.20

### Example 84

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valyl]-L-phenylalanamide, fumarate (2:3) salt



A solution of Compound 62 (153 mg; 0.185 mmol) in 2 ml of HOAc was stirred for 1 h over 20% Pd(OH)<sub>2</sub>/C (50 mg) at RT under a H<sub>2</sub> atmosphere (balloon). The catalyst was removed by filtration through a 0.45 micron Nylon-66 filter and the filtrate was concentrated to dryness. The residue was dissolved in 5 ml of MeOH and fumaric acid (43 mg; 0.370 mmol) was added as a solution in hot MeOH. The MeOH was removed *in vacuo* and the residual HOAc was azeotroped with heptane. After drying under high vacuum for several hours, the solid was dissolved in ~2 ml of MeOH and Et<sub>2</sub>O (~12 ml) was added dropwise with rapid stirring. The resulting suspension was filtered and dried under high vacuum at 60°C for 48 h to give 149 mg (93%) of Compound 84 as a white powder.

mp 125-136°C;  $[\alpha]_D = -20.7$  (c 0.15, MeOH).

Mass Spec. FAB + ions: M+H = 690.

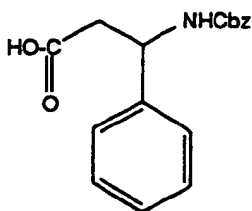


Analysis calc. for $C_{39}H_{55}N_5O_6 \cdot 1.5 C_4H_4O_4 \cdot 0.52 H_2O$ :			
	C, 61.89;	H, 7.16;	N, 8.02;
Found:	C, 61.91;	H, 7.23;	N, 8.00.

### Example 85

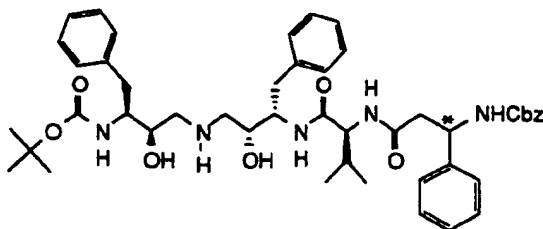
Preparation of [S-(1R\*,2S\*,3R\*)]-N<sup>2</sup>-[3-[[[(Phenylmethoxy)carbonyl]amino]-1-oxo-3-phenylpropyl]-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)-propyl]-L-valinamide (Compound 85b)

#### (a) Compound 85a



Benzylchloroformate (1.0 ml; 6.70 mmol) and 2N NaOH (3.1 ml; 6.2 mmol) were alternately added over 5 min to a vigorously stirred solution of 3-amino-3-phenylpropionic acid (1.0 g; 6.05 mmol) in 3.05 ml of 2N NaOH at 0°C. The mixture was stirred for 30 min at 0°C and 30 min at RT. 1N NaOH (10 ml) and water (50 ml) were added and the reaction mixture was washed with Et<sub>2</sub>O (3 x 50 ml). After acidifying the aqueous layer to pH <1 with 6N HCl, it was extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub>, and concentrated to a white solid which was recrystallized from EtOAc:hexane, 1:1 to afford 1.02 g (61%) of Compound 85a.

#### (b) Compound 85b

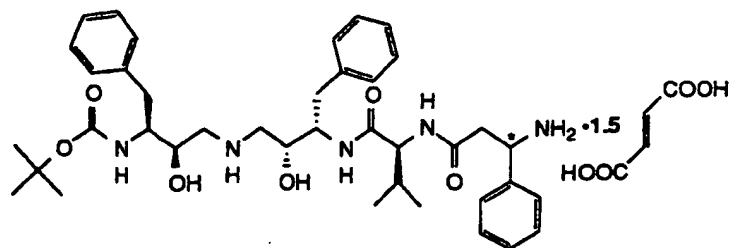


The title Compound 85b (white solid) was prepared as a mixture of diastereomers (at carbon marked with an asterisk) from Compounds 61 and 85a by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>; 70°C): δ 0.57 (d, J= 7 Hz, 1.5H), 0.63 (d, J= 7 Hz, 1.5H), 0.69 (d, J= 7 Hz, 1.5H), 0.72 (d, J= 7 Hz, 1.5H), 1.25 (s, 9H), 2.56 (m, 8H), 2.95 (m, 2H), 3.43 (m, 2H), 3.57 (m, 1H), 3.91 (m, 1H), 4.04 (m, 2H), 4.55 (brs, 1H), 4.97 (m, 3H), 6.33 (brs, 1H), 7.25 (m, 20H), 7.50 (m, 2H), 7.56 (d, 8.5 Hz, 1H).

### Example 86

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>(3-Amino-1-oxo-3-phenylpropyl)-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide, fumarate (2:3) salt (Compound 86)



Compound 85b was converted to the title Compound 86 (white solid) by a procedure analogous to that used for the synthesis of Compound 84.

mp 138-146°;  $[\alpha]_D = -13.0$  (c 0.2, MeOH).

Mass Spec. FAB+ ion : (M+H) = 690.

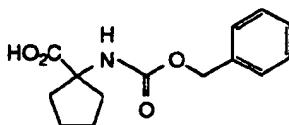
Analysis calc. for  $C_{39}H_{55}N_5O_6 \cdot 1.5 C_4H_4O_4 \cdot 0.92 H_2O$ :

	C, 61.98;	H, 7.15;	N, 8.03;
Found:	C, 61.95;	H, 7.21;	N, 8.06.

#### Example 87

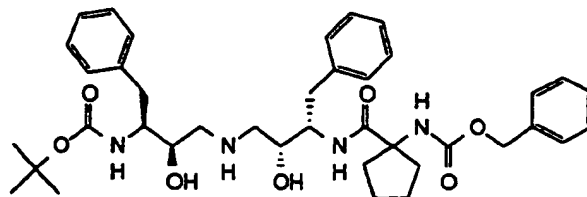
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[1-[(phenylmethoxy), carbonyl]amino]cyclopentyl]carbonyl]amino]-4-phenylbutyl]-amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl-ethyl ester (Compound 87b)

##### (a) Compound 87a



Compound 87a was prepared from 1-aminocyclopentanecarboxylic acid (cycloleucine) by a procedure analogous to that used for the synthesis of Compound 85a.

##### (b) Compound 87b



The title Compound 87b was prepared from Compounds 54 and 87a by a procedure analogous to that used for the synthesis of Compound 55.

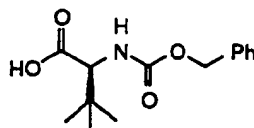
mp 70-73°C;  $[\alpha]_D = +9^\circ$  (c 0.2, MeOH);

Mass Spec: FAB (M + H)+: 689.

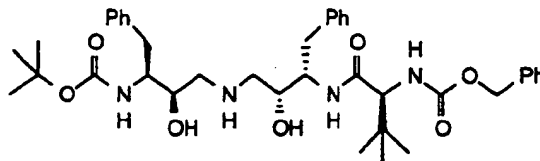
Analysis calculated for $C_{38}H_{52}N_4O_7 \cdot 0.65H_2O$ :			
	C, 66.87;	H, 7.67;	N, 8.00;
Found:	C, 66.82;	H, 7.58;	N, 8.05.

**Example 88**

Preparation of [1S-[1R\*-[1R\*,2S\*(2S\*,3R\*)]]]-2,2-Dimethyl-1-[[[3-[[[3-[(1,1-Dimethylethoxy)carbonylamino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-carbonyl]propyl]carbamic acid, phenylmethyl ester (Compound 88b)

**(a) Compound 88a**

Compound 88a was prepared from L-tert-leucine by a procedure analogous to that used for the synthesis of Compound 85a.

**(b) Compound 88b**

The title Compound 88b was prepared from Compounds 54 and 88a by a procedure analogous to that used for the synthesis of Compound 55 (DMF only was used along with 1 equivalent of N-methylmorpholine).  
m.p. 144-147°;  $[\alpha]_D^{25} = 14.8^\circ$  (c 0.15, MeOH)  $[\alpha]_{365} = -62.7^\circ$  (c 0.15, MeOH).  
Mass Spec.: (FAB/SIMS): 691 (M+H).

Analysis Calc. For $C_{39}H_{54}N_4 \cdot 0.13 H_2O$ :			
	C, 67.58;	H, 7.89;	N, 8.08
Found:	C, 67.32;	H, 7.76;	N, 8.34

**Example 89**

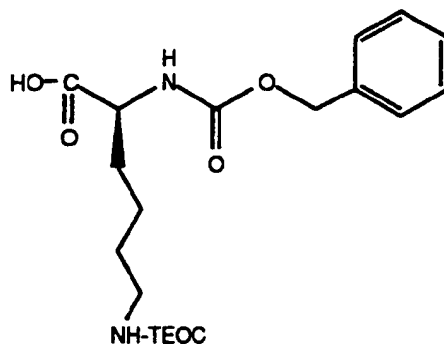
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[3-[(1,1-Dimethylethoxy)carbonylamino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-lysineamide (Compound 89b)

(a) Compound 89a

5

10

15



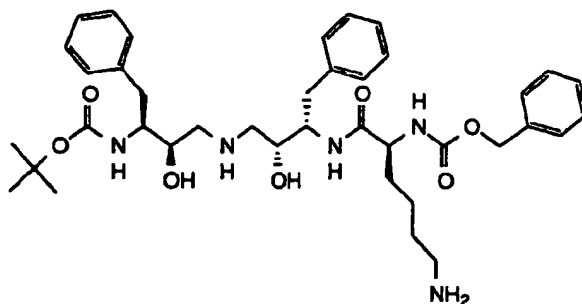
Compound 89a was prepared from  $\alpha$ -N-Cbz-L-lysine and trimethylsilylethylchloroformate by a procedure analogous to that used for the synthesis of Compound 85a.

20

(b) Compound 89b

25

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35

The title Compound 89b (white solid) was prepared from Compounds 48 and 89a by a two-step procedure analogous to that used for the synthesis of Compound 52 (6 equivalents of  $n\text{-Bu}_4\text{NF}$  was used).  
mp 129-131°C;  $[\alpha]_D^{25} = -19.4^\circ$  (c 0.35, MeOH).  
Mass Spec. FAB + ion: (M + H) = 706.

40

Analysis calc. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_7 \cdot 1.49\text{H}_2\text{O}$ :			
	C, 63.93;	H, 7.98;	N, 9.56;
Found:	C, 64.01;	H, 7.68;	N, 9.48.

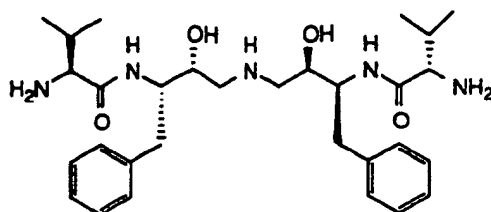
45

Example 90

50

Preparation of [S-(1R\*,2S\*)-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[L-valinamide], trihydrochloride (Compound 90)

55

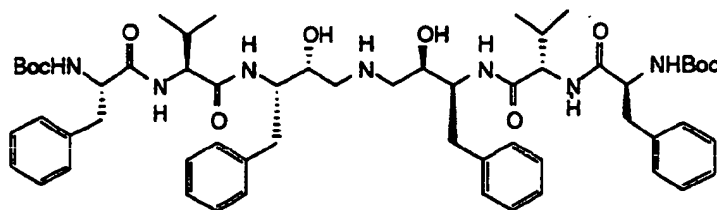


.3HCl

The title Compound 90 was prepared from Compound 34 by a procedure analogous to that used for the synthesis of Compound 32.  $R_f = 0.29$  (20:2:78 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>).

#### Example 91

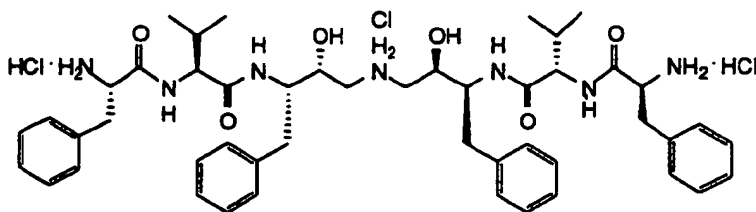
Preparation of [S-(1R\*,2S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[N<sup>2</sup>-[N-[(1,1-dimethoxyethyl)carbonyl]-L-phenylalanyl]-L-valinamide] (Compound 91)



The title Compound 91 was prepared from Compound 90 and Boc-L-phenylalanine by a procedure analogous to that used for the synthesis of Compound 75f.  $R_f = 0.31$  (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>). MS: (FAB): 1036 (M+H).

#### Example 92

Preparation of [S-(1R\*,2S\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[N<sup>2</sup>-(L-phenylalanyl)-L-valinamide], trihydrochloride (Compound 92)



Compound 91 (81 mg; 78.2  $\mu$ mol) was stirred with methanolic HCl (1 ml of 2.09M solution) at 0°C for 30 min and at RT for 2 h. The volatiles were removed and the residue evaporated from Et<sub>2</sub>O and dried under high vacuum overnight. The resulting solid was dissolved in MeOH and precipitated with Et<sub>2</sub>O after which it was triturated with Et<sub>2</sub>O and EtOAc to give 62 mg (86%) of a light-orange colored solid. m.p. dec. 180-187°C;  $[\alpha]_D^{25} = -16.5^\circ$  (c 0.12, MeOH); MS: (FAB): 836 (M+H).

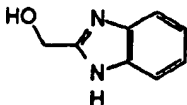
Anal. Calc. for C<sub>48</sub>H<sub>68</sub>Cl<sub>3</sub>N<sub>7</sub>O<sub>8</sub> · 2.58 H<sub>2</sub>O:

	C, 58.13;	H, 7.43;	N, 9.88
Found:	C, 58.20;	H, 7.33;	N, 9.81

## Exempl 93

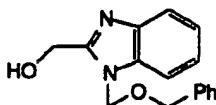
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amin]-2-hydroxy-1-(phenylmethyl)propyl]-N2-[[[1H-benzimidazol-2-ylmethoxy)carbonyl]-L-valinamide (Compound 93f)

## (a) Compound 93a



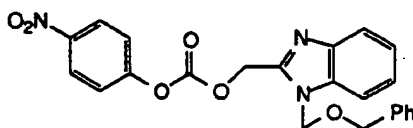
A mixture of 3.24 g (30.0 mmol) of *o*-phenylenediamine and 3.42 g (45.0 mmol) of glycolic acid in 30 mL of 4N HCl was heated at reflux for 45 min. The resulting solution was cooled to RT and basified (pH=8) with NH<sub>4</sub>OH. The resulting suspension was cooled in an ice bath, and the solid filtered, rinsed with cold H<sub>2</sub>O and recrystallized from H<sub>2</sub>O to afford 2.70 g (61%) of Compound 93a as a tan solid.

## (b) Compound 93b



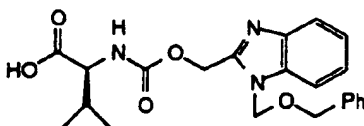
To a solution of 500 mg (3.37 mmol) of Compound 93a in 5 mL of DMF were added 357 mg (3.37 mmol) of Na<sub>2</sub>CO<sub>3</sub> and 0.58 mL (3.37 mmol; 80% pure) of benzyl chloromethyl ether. The mixture was stirred at 0°C for 1 h and at RT for 24 h. The mixture was partitioned between EtOAc and H<sub>2</sub>O, and the combined organic extracts dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 945 mg of crude material. Flash chromatography on silica gel (25-100% EtOAc-hexane; then, 5% CH<sub>3</sub>OH-EtOAc) provided 339 mg (39%) of Compound 93b.

## (c) Compound 93c



To a solution of 260 mg (1.01 mmol) of Compound 93b in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> and 1.5 mL of pyridine at 0°C was added 214 mg (1.06 mmol) of *p*-nitrophenylchloroformate in 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at 0°C for 1 h and at RT for 3 h, diluted with 100 mL of EtOAc and washed with 1M NaOH (3 x 25 mL), H<sub>2</sub>O (2 x 25 mL), and brine (25 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo* affording 396 mg of Compound 93c.

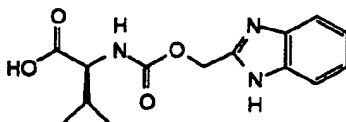
## (d) Compound 93d



To a solution of 105 mg (0.893 mmol) of L-valine in 0.9 mL of 1.0N NaOH was added a solution of 387 mg

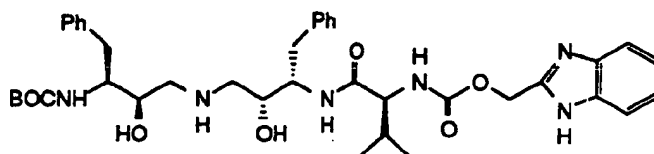
(0.893 mmol) of Compound 93c in 3 mL of dioxane and 0.2 mL of Et<sub>3</sub>N. The mixture was stirred at RT for 18 h and partitioned between EtOAc and H<sub>2</sub>O. The aqueous layer was acidified to pH=4 with 5% KHSO<sub>4</sub> and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated *in vacuo* to provide 0.79 g of crude acid. Flash chromatography on silica gel, eluting with 50% EtOAc-hexane and then 10% MeOH-CHCl<sub>3</sub>, afforded 151 mg (41%) of Compound 93d.

(e) Compound 93e



To a solution of 242 mg (0.588 mmol) of Compound 93d in 3 mL of MeOH was added a solution of HCl (0.74 mmol) in 5 mL of MeOH and 200 mg of Pd(OH)<sub>2</sub>. The mixture was stirred under a H<sub>2</sub> atmosphere (balloon) for 4 h at which time an additional 0.1 mL of 1N HCl and 50 mg of Pd(OH)<sub>2</sub> was added. The mixture was stirred under a H<sub>2</sub> atmosphere for another 2.5 h and then filtered and evaporated *in vacuo*. Re-evaporation *in vacuo* from CHCl<sub>3</sub>/Et<sub>2</sub>O afforded 326 mg of crude Compound 93e as an HCl salt.

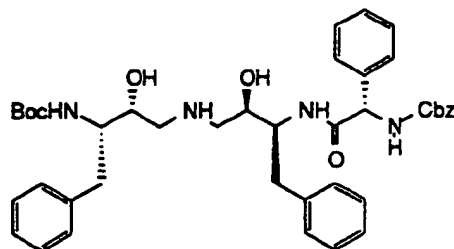
(f) Compound 93f



To a solution of 270 mg (~0.488 mmol; ca. 60% pure, contaminated with solvent) of Compound 93e in 3 mL of dry DMF at 0°C were added 228 mg (0.488 mmol) of Compound 54, 99 mg (0.73 mmol) of HOBT, 110 μL of N-methylmorpholine, and 104 mg (0.54 mmol) of EDC. The mixture was stirred at RT for 18 h, diluted with 100 mL of EtOAc, and washed with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo* to give 0.41 g of crude material. Flash chromatography on silica gel (5% CH<sub>3</sub>OH/CHCl<sub>3</sub>, then 5-7.5% CH<sub>3</sub>OH/CHCl<sub>3</sub> with 0.5% NH<sub>4</sub>OH) followed by precipitation from hot MeOH with Et<sub>2</sub>O provided 150 mg of the title Compound 93f. mp 161-165°C; Mass Spec. 717 (M+H)<sup>+</sup>

Example 94

Preparation of [1S-[[1R\*-[1R\*,2S\*(2S\*,3R\*)]]]-[2-[[3-[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2-oxo-1-phenylethyl]carbamic acid, phenylmethyl ester (Compound 94)



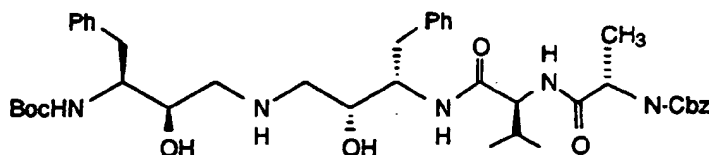
The title Compound 94 was prepared from Compound 54 and Cbz-L-phenylglycine by a procedure analogous to that used for the preparation of Compound 55 (DMF only used along with 2 eq. N-methylmorpholine). m.p. 203.5 - 205°C; [α]<sub>D</sub> = +16.2° (c 0.22, AcOH)

Elemental Analysis  
(%) for  $C_{41}H_{50}N_4O_7 \cdot 0.24 H_2O$

	Calc.	F und
C	68.86	68.98
H	7.11	7.13
N	7.83	7.71

#### Example 95

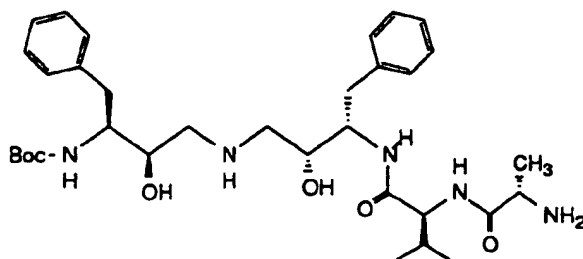
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[N-[(phenylmethoxy)carbonyl]-L-alanyl]-L-valinamide (Compound 95)



The title Compound 95 was prepared from Compound 61 and Cbz-alanine by a procedure analogous to that used for the two-step conversion of Compound 48 to Compound 52.

#### Example 96

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(L-alanyl)-L-valinamide, fumarate salt (Compound 96)



Fumaric acid salt

Compound 95 was converted into Compound 96 by a procedure analogous to the one used for the synthesis of Compound 84.

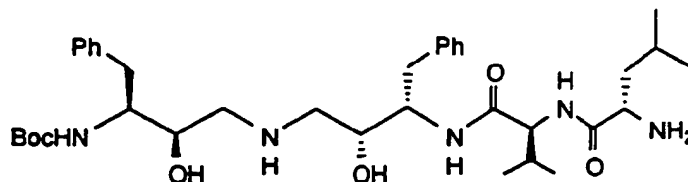
mp 168-174°C;  $[\alpha]_D^{22} = -19^\circ$  (c 0.15,  $CH_3OH$ )

High Resolution Mass Spec. (FAB):  $C_{33}H_{52}N_5O_8 = 614.3908^+$ ;  $\Delta = 1.6$  ppm.

#### Example 97

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[N-[(phenylmethoxy)carbonyl]-L-leucyl]-L-valinamide (Compound 97)

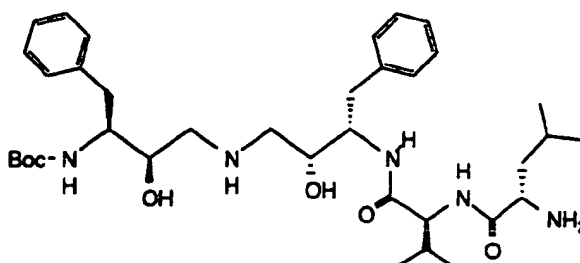




The title Compound 97 was prepared from Compound 61 and Cbz-L-leucine by a procedure analogous to that used for the two-step conversion of Compound 48 to Compound 52.

#### Example 98

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(L-leucyl)-L-valinamide, fumarate salt (Compound 98)



fumarate salt

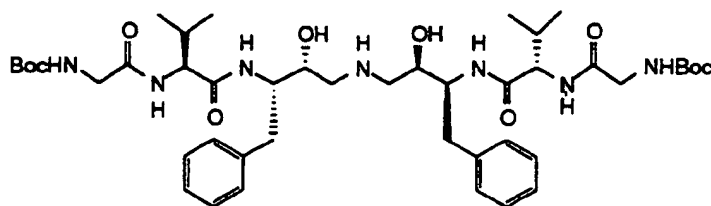
Compound 97 was converted into Compound 98 by a procedure analogous to the one used for the synthesis of Compound 84.

mp 184-190°C;  $[\alpha]_D^{22} = -12^\circ$  (c 0.16, CH<sub>3</sub>OH)

High Resolution Mass Spec. (FAB): C<sub>36</sub>H<sub>57</sub>N<sub>5</sub>O<sub>8</sub> = 656.4382<sup>+</sup>;  $\Delta = 0.8$  ppm.

#### Example 99

Preparation of [S-(1R\*,2S\*)]-N,N'-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[N<sup>2</sup>-[[[(1,1-dimethylethoxy)carbonyl]amino]acetyl]-L-valinamide] (Compound 99)



The title Compound 99 was prepared from Compound 90 and Boc-glycine by a procedure analogous to the one used for the synthesis of 75f.

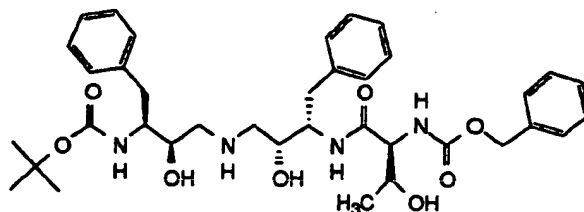
m.p. 212 - 215°C;  $[\alpha]_D = -26.2^\circ$  (c 0.1, AcOH)

Elemental Analysis  
(%) for  $C_{44}H_{69}N_7O_{10} \cdot 0.78 H_2O$

	Calc.	Found
C	60.74	60.81
H	8.17	8.08
N	11.27	11.20

### Example 100

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[(phenylmethoxy)carbonyl]-L-threoninamide (Compound 100)



The title Compound 100 (white solid) was prepared from Compound 54 and Cbz-L-threonine by a procedure analogous to that used for the synthesis of 55 (DMF only used).  
m.p. 150 - 155°C;  $[\alpha]_D = -17.8^\circ$  (C 0.18, MeOH)  
Mass Spec.: 679 (M+H)

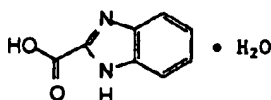
Elemental Analysis  
(%) for  $C_{37}H_{50}N_4O_8 \cdot 0.75 H_2O$

	Calc.	Found
C	64.20	64.25
H	7.50	7.34
N	8.09	8.04

### Example 101

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[(1H-benzimidazol-2-yl)-carbonyl]-L-valinamide (Compound 101b)

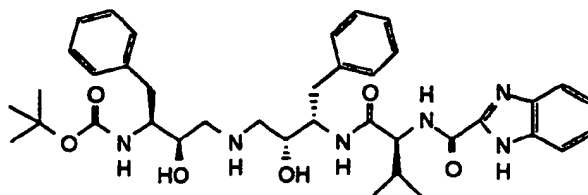
(a) Compound 101a



To a solution of 0.500 g (3.37 mmol) of Compound 93a in 10 mL of boiling  $H_2O$  was added 10 drops of 3M

NaOH. The resulting solution was kept at 100°C during the addition (10 min) of a solution of 0.8 g (5.05 mmol) of  $\text{KMnO}_4$  in 50 mL of water. Heating at 100°C was continued for 30 min. The hot mixture was filtered through celite, cooled to RT and acidified with HOAc. The white precipitate was collected by suction filtration and recrystallized from  $\text{H}_2\text{O}$  to afford 185 mg (34%) of Compound 101a. mp 170-172°C ( $-\text{CO}_2$ ).

(b) Compound 101b



The title Compound 101b was prepared from Compounds 61 and 101a by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

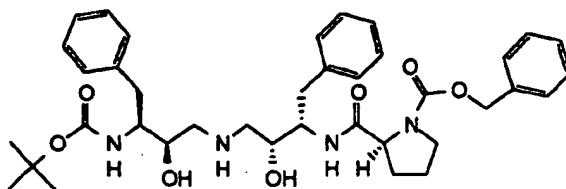
m.p. 210-215°C;  $[\alpha]_D^{20} = -30^\circ$  (c 0.32,  $\text{CH}_3\text{OH}$ )

Mass Spec. 687 ( $\text{M}+\text{H}$ )<sup>+</sup>

Elemental Analysis (%) $\text{C}_{38}\text{H}_{50}\text{N}_8\text{O}_8$		
	Calc.	Found
C	66.45	66.53
H	7.34	7.38
N	12.24	12.21

Example 102

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[[[3-[[[3-[[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[phenylmethoxy)carbonyl]-L-prolinamide (Compound 102)



The title Compound 102 (white solid) was prepared from Compound 54 and Cbz-L-proline by a procedure analogous to that used for the synthesis of Compound 55 (used DMF only).

m.p. 142 - 146°C;  $[\alpha]_D = -31.7^\circ$  (C 0.81, MeOH)

Mass Spec. 675 ( $\text{M}+\text{H}$ )

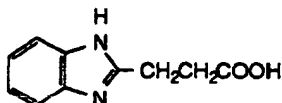
El mental Analysis  
(%) for  $C_{38}H_{50}N_4O_7 \cdot$   
 $0.69 H_2O$

	Calc.	Found
C	66.42	66.29
H	7.53	7.41
N	8.15	8.28

### Example 103

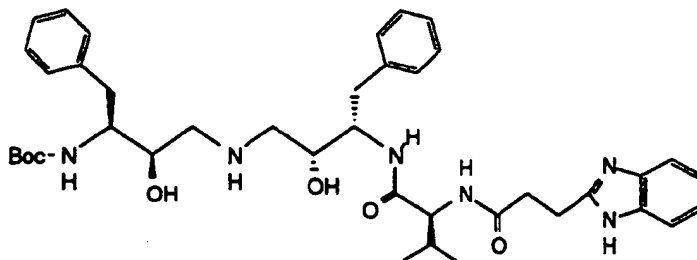
Preparation of [S-(1R\*,2S\*(2S\*,3R\*))]-N<sup>2</sup>-[3-(1H-Benzimidazol-2-yl)-1-oxo-propyl]-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 103b)

#### (a) Compound 103a



A mixture of *o*-phenylenediamine (2.70 g, 25 mmol) and succinic acid (5.02 g, 42.5 mmol) was heated at reflux in 150 ml of 5 N HCl for 3 hrs. The mixture was allowed to stand overnight at RT, filtered and then the pH was adjusted to 5 with 5 N NaOH. The aqueous mixture was saturated with NaOAc and stored overnight at 0°C. The crude product precipitated as a tan solid and was crystallized from H<sub>2</sub>O/EtOH (9:1) affording 968 mg (20%) of the Compound 103a. See Chemical Abstracts CA: 19953g (1961); French Patent 1,179,933 (May 29, 1959).

#### (b) Compound 103b



The title Compound 103b was prepared from Compounds 61 and 103a by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.  
mp 182-185°C;  $[\alpha]_D^{22} = -20^\circ$  (c 0.25, CH<sub>3</sub>OH)

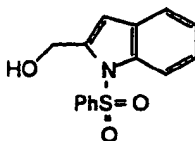
Analysis calc. for  $C_{40}H_{54}N_8O_8 \cdot 2.5 \text{ mole } H_2O$ :

	C, 63.22;	H, 7.80;	N, 11.06;
Found:	C, 63.06;	H, 7.47;	N, 10.90.

## Exempl 104

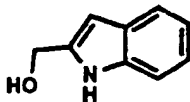
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(1H-indol-2-ylmethoxy)carbonyl]-L-valinamid (Compound 104e)

## (a) Compound 104a



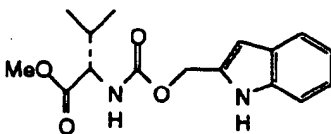
A solution of LiBH<sub>4</sub> (1.6M in THF, 2.4 mL, 3.8 mmol) was added at -78°C to a stirred solution of 1.0 g, 3.5 mmol, of 2-formyl-1-phenylsulfonyl indole (Saulnier et al., *J. Org. Chem.*, 47, 757 (1982)) in 30 mL of Et<sub>2</sub>O. The mixture was allowed to come to RT and stirred for 30 min. The reaction mixture was carefully quenched by adding sat. NaHCO<sub>3</sub>, diluted with EtOAc and stirred for 30 min. The organic layer was separated, dried over MgSO<sub>4</sub> and concentrated to afford 0.975 g (97%) of Compound 104a.

## (b) Compound 104b

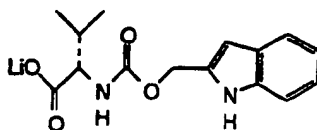


To a solution of Compound 104a (0.97 g, 3.38 mmol) in 15 mL 2-methoxyethanol was added 3 mL 20% aq. KOH. The mixture was heated under reflux for 3 h, allowed to come to RT and partitioned between EtOAc and brine. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude brown oil which was purified by flash chromatography (silica gel/hexane-EtOAc 5:1 to 1:1) giving 0.45 g (91%) of Compound 104b as a yellow solid.

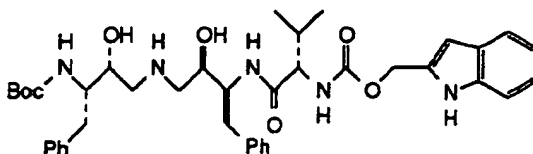
## (c) Compound 104c



Trichloromethyl chloroformate (1.08 mL) was added to a stirred suspension of L-valine methyl ester hydrochloride (3.0 g, 17.9 mmol) in 10 mL dry dioxane. The mixture was refluxed for 1.5 h, concentrated, and the residue flash distilled (bath temperature 100-125°C, 0.5 mm vacuum) to afford 1.0 g of L-valine methyl ester isocyanate. A solution of 0.55 g (3.5 mmol) of L-valine methyl ester isocyanate in 7.5 mL dry toluene was treated with 4M HCl in dioxane (79 mL, 0.315 mmol) at RT and stirred for 5 min. The resulting mixture was treated with 1.0 g solid K<sub>2</sub>HPO<sub>4</sub> for 5 min, followed by the addition of Compound 104b (0.464 g, 3.15 mmol). The mixture was refluxed for 9 h, diluted with EtOAc and washed with sat. NaHCO<sub>3</sub> followed by brine. The organic phase was dried (MgSO<sub>4</sub>), concentrated, and the crude product purified by flash chromatography (silica gel/hexane to EtOAc-hexane 1:9 to 1:4, stepwise gradient) to afford 0.51 g (53%) of Compound 104c as a yellow gummy solid.

(d) Compound 104d

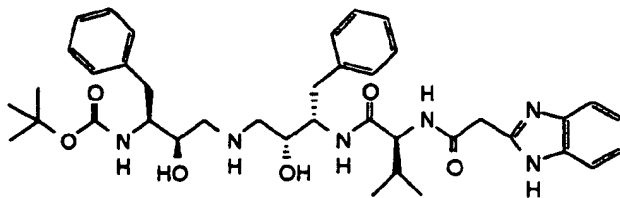
To a solution of Compound 104c (0.5 g, 1.64 mmol) in 7 mL dioxane was added 0.54 M aq. LiOH (3.05 mL, 1.64 mmol), stirred at RT for 12 h, concentrated and the residue chased 3 times with toluene. The resulting off-white Li salt (0.5 g) of the acid was used as such for the next step.

(e) Compound 104e

To a solution of Compound 104d (0.15 g, 0.51 mmol) and HOBT (0.101 g, 0.66 mmol) in 1.5 mL dry DMF at 0°C was added EDC (0.108 g, 0.56 mmol) and N-methyl morpholine (0.111 mL, 1.02 mmol), and the resulting mixture was stirred at 0°C for 1 h. The mixture was treated with Compound 54 (0.226 g, 0.51 mmol), and stirred at RT for 12 h, concentrated, and the residue partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, concentrated, and the crude product was purified by flash chromatography (silica gel/CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH 99:1:0.5 to 90:10:1) followed by preparative HPLC (Waters Prep Nova-Pack HR C18, 6 micron, 30X300 mm; eluent: MeOH-H<sub>2</sub>O-TFA 75:25:0.05 to 80:20:0.05; UV 254 nm). The desired fractions were made basic with sat. NaHCO<sub>3</sub>, concentrated, and the residue partitioned between EtOAc/1:1 brine-sat. NaHCO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub>, concentrated and the resulting white solid was triturated from 10:1 hexane-Et<sub>2</sub>O to afford 0.181 g (50%) of the title Compound 104e as a white solid. [α]<sub>D</sub> = +3.0° (c = 0.5, CH<sub>2</sub>Cl<sub>2</sub>); m.p. 115 - 120°C  
High Resolution Mass Spectrum: (M+H)<sup>+</sup> = 716.4010, Δ 1.8 ppm error (theoretical: (M+H)<sup>+</sup>: 716.5023).

Example 105

Preparation of S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(1H-benzimidazol-2-ylacetyl)-L-valinamide (Compound 105)



The title Compound 105 was prepared from Compound 61 and 2-benzimidazoleacetic acid (Copeland et al., *J. Am. Chem. Soc.*, 65, 1072 (1943)) by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.  
m. p. 177-182°C; Mass spec (FAB) 701 (M+H)

Elemental Analysis Calc. for $C_{39}H_{52}N_6O_8 \cdot 0.78 H_2O$			
	C, 65.52;	H, 7.55;	N, 11.75
Found	C, 65.52;	H, 7.40;	N, 11.68

5

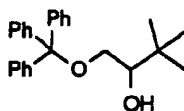
10 Example 106

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[3,3-Dimethyl-1-oxo-2-(phenylmethoxy)butyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 106e)

15

(a) Compound 106a

20

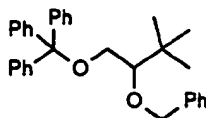


A solution of 1.18 g (10 mmoles) of 3,3-dimethyl-2-hydroxy-1-butanol and 3.1 g of triphenylmethyl chloride in 25 ml of pyridine was stirred at RT overnight. The reaction mixture was evaporated to dryness and the residue diluted with EtOAc and washed with 1N HCl, brine, saturated  $NaHCO_3$  and brine. After drying ( $MgSO_4$ ), removal of solvent gave an oily residue which was purified by flash chromatography on a 400cc column of silica gel. Elution with 5% ether-hexane afforded 3.0 g (8.5 mmoles, 85% yield) of Compound 106a as a clear colorless oil which crystallized on standing.

30

(b) Compound 106b

35

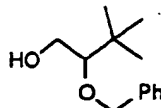


To a solution of 750 mg (2.1 mmoles) of Compound 106a in 9 ml of dry THF, at  $-10^\circ C$  was added dropwise 4.6 ml (2.3 mmoles) of 0.5M  $KN(TMS)_2$  in toluene. Cooling was removed and the clear solution stirred for 0.5 hr. The reaction was ice cooled and 309  $\mu l$  (2.6 mmoles) of benzyl bromide was added dropwise, neat. Stirring was continued at RT for 1 hr. The reaction was diluted with brine and extracted with EtOAc. The extracts were washed with brine, dried ( $MgSO_4$ ) and the solvent evaporated to yield an oily residue which was purified by flash chromatography on a 450cc column of silica gel. Elution with 20%  $CH_2Cl_2$ -hexane gave 880 mg (1.95 mmoles, 94% yield) of Compound 106b as a colorless oil.

45

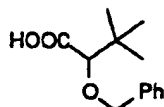
(c) Compound 106c

50

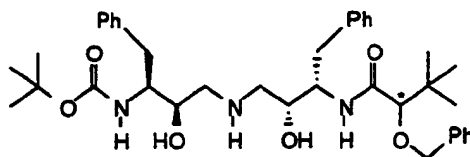


A solution of 0.8 g (1.8 mmoles) of Compound 106b and 40 mg of *p*-toluenesulfonic acid in 20 ml of MeOH was stirred at RT for 3 hr. The reaction was evaporated to dryness and the residue placed on a 400cc column of silica gel. Elution with 20%  $Et_2O$ -hexane, followed by 30%  $Et_2O$ -hexane gave 233 mg (1.12 mmol, 63%) of Compound 106c as a clear colorless oil.

55

(d) Compound 106d

To a solution of 5.8 g (16.8 mmoles) of pyridinium dichromate in 8 ml of DMF at RT was added dropwise a solution of 1.0 g (4.8 mmoles) of Compound 106c in 2 ml of DMF. The dark solution was stirred overnight, poured into 80 ml of ice/water and extracted with Et<sub>2</sub>O. The extracts were filtered through a Celite-MgSO<sub>4</sub> mixture and extracted with saturated NaHCO<sub>3</sub>, and H<sub>2</sub>O. The combined aqueous fractions were washed once with Et<sub>2</sub>O, acidified with 6N HCl, and extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>) and the solvent removed to yield 480 mg of clear colorless oil. Distillation (kugelrohr, 140°C, 0.05 mm) gave 410 mg (1.8 mmoles, 38%) of Compound 106d as a clear colorless oil.

(e) Compound 106e

\*mixture of diastereomers

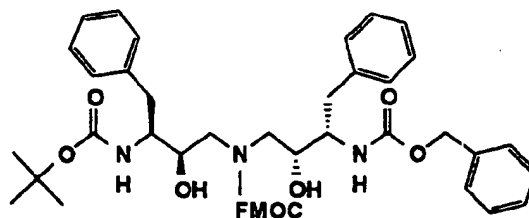
The title Compound 106e was prepared as a white solid from Compounds 54 and 106d by a procedure analogous to that used for the synthesis of Compound 55 (DMF only; 2 eq. of N-methyl-morpholine used). m.p. 114-117°C; Mass spec. (M+H) 648

Elemental Analysis Calc. for C<sub>38</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub>:

	C, 70.45;	H, 8.25;	N, 6.49
Found:	C, 70.09;	H, 8.27;	N, 6.57

Example 107

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]-[3-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester (Compound 107)



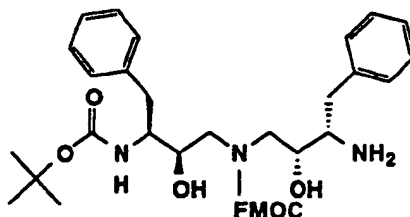
Compound 45 was converted to the title Compound 107 by a procedure analogous to the one used for the synthesis of Compound 39.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.23 (m, 9H), 2.42 (m, 1H), 2.59 (m, 1H), 2.91 (m, 1H), 3.07 (m, 1H), 3.18 (m, 1H), 3.28 (m, 1H), 3.44 - 3.88 (m's, 6H), 4.27 (m, 1H), 4.52 (m, 2H), 4.87 (m, 2H), 7.05 - 7.47 (m's, 19H), 7.64 (m, 2H), 7.78 (m, 2H).



## Exempl 108

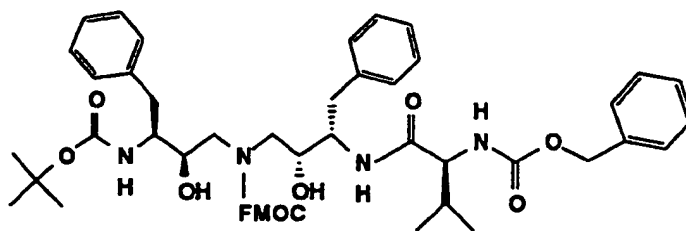
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[(3-Amino-2-hydroxy-4-phenylbutyl)-[(9H-fluoren-9-yl-methoxy) carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 108)



Compound 107 was converted to the title Compound 108, by a procedure analogous to that used for the synthesis of Compound 61 (EtOH was employed in place of MeOH). Compound 108 was used without further purification in the preparation of Compound 109 following.

## Example 109

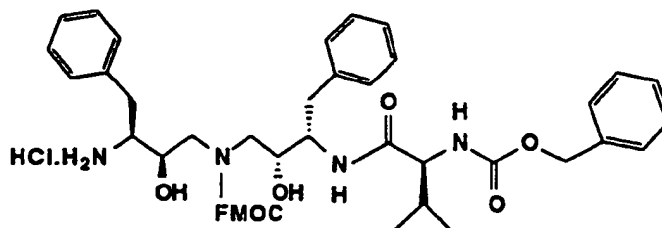
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]][(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy) carbonyl]-L-valinamide (Compound 109)



Compound 108 was coupled with Cbz-valine by a procedure analogous to that used for the preparation of Compound 51 to give the title Compound 109.  
Mass Spec. (FAB): 899 (M + H)<sup>+</sup>.

## Example 110

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-3-[[3-[(3-Amino-2-hydroxy-4-phenylbutyl)-[(9H-fluoren-9-yl-methoxy) carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide, monohydrochloride (Compound 110)

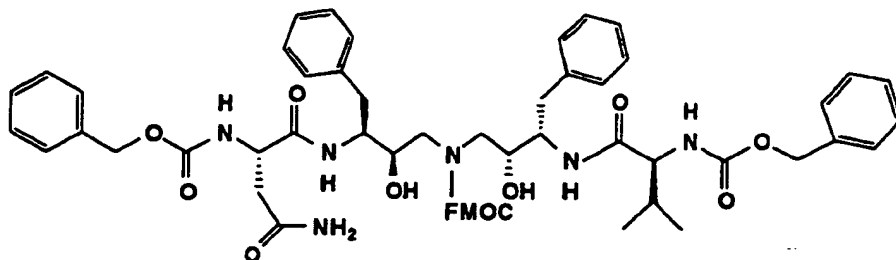


Acetyl chloride (39.8  $\mu$ L, 56.0 mmol, 10 eq.) was added at 0°C to MeOH (560  $\mu$ L) followed by Compound 109 (50 mg, 0.56 mmol). The viscous solution was diluted with 1 mL MeOH and an additional solution of acetyl chloride (39.8  $\mu$ L) in MeOH (2 mL) was added. The white turbid mixture was allowed to warm to RT, stirred for 4 hrs, and then gently warmed to 40°C. After 1 h, the volatiles were removed *in vacuo* to yield 46 mg (99%)

of Compound 110 which was used without further purification.

#### Example 111

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[2-Hydroxy-3-[[2-hydroxy-4-phenyl-3-[[N-[(phenylmethoxy)carbonyl]-L-valyl]amino]butyl][(9H-fluoren-9-yl-methoxy)carbonyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-asparaginamide (Compound 111)

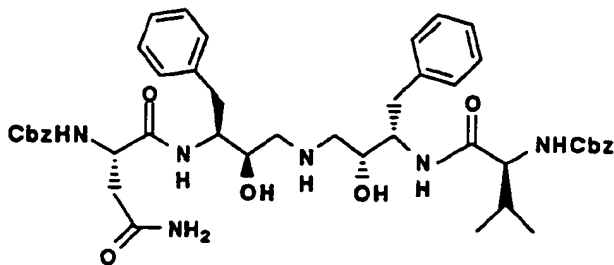


Compound 110 and Cbz-L-asparagine were reacted by a procedure analogous to that used for the preparation of Compound 51 to give the title Compound 111.

Mass Spec.: (FAB): 1047.5 (M + H)<sup>+</sup>.

#### Example 112

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[2-Hydroxy-3-[[2-hydroxy-4-phenyl-3-[[N-[(phenylmethoxy)carbonyl]-L-valyl]amino]butyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-asparaginamide, monohydrochloride (Compound 112)



HCL

Compound 111 was converted to the title Compound 112 by a procedure analogous to that used for the synthesis of Compound 42. Compound 112 was isolated as the HCl salt which was recrystallized from MeOH/Et<sub>2</sub>O.

mp 198 - 200°C; [α]<sub>D</sub> = -31° (c 0.2, AcOH).

Mass Spec.: (FAB): 825 (M + H)<sup>+</sup>.

Analysis calculated for C<sub>46</sub>H<sub>56</sub>N<sub>6</sub>O<sub>9</sub>·HCl·2.30H<sub>2</sub>O:

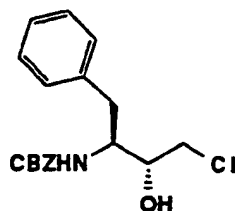
	C, 59.93;	H, 6.77;	N, 9.32;
Found:	C, 60.26;	H, 6.56;	N, 8.99;

#### Example 113

Preparation of [1S-[1R\*,2S\*(2R\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbu-

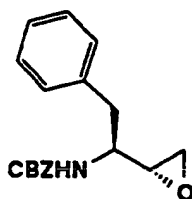
tyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester (Compound 113c)

(a) Compound 113a



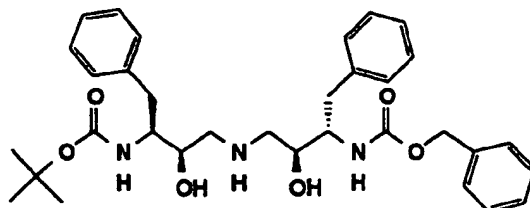
Compound 113a was prepared during the reduction procedure in which Compound 44a above was prepared and isolated.

(b) Compound 113b



Compound 113b was prepared from Compound 113a by a procedure analogous to that used for the synthesis of Compound 1b(ii).

(c) Compound 113c

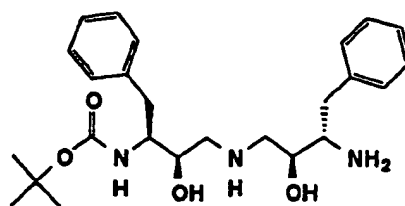


Compounds 113b and 16b (1 eq. of each) were reacted by a procedure analogous to that used for the synthesis of Compound 4b to give the title Compound 113c (white solid).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.29 (s, 9H), 2.56 (dd, J= 10.5, 14 Hz, 1H), 2.66 (m, 2H), 2.80 (m, 3H), 2.91 (dd, J= 5.5, 13.5 Hz, 1H), 3.09 (dd, J= 3.5, 14 Hz, 1H), 3.60 (m, 2H), 3.80 (m, 1H), 3.86 (m, 1H), 4.99 (m, 2H), 7.20 (m, 15H).

Example 114

Preparation of [1S-[1R\*,2S\*(2R\*,3R\*)]-[3-[(3-Amino-2-hydroxy-4-phenylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 114)

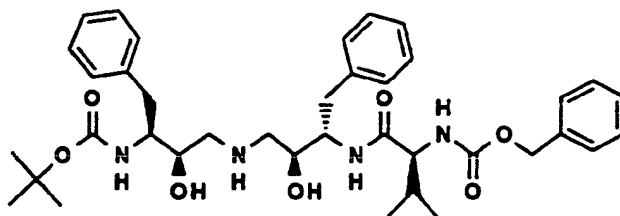


Compound 113c was converted to the title Compound 114 (white foam) using conditions analogous to those used for the synthesis of Compound 7.

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.29 (s, 9H), 2.54 (dd, J= 10.5, 14 Hz, 1H), 2.63 (dd, J= 7.5, 12 Hz, 1H), 2.71 (m, 2H), 2.85 (dd, J= 9.5, 12.5 Hz, 1H), 2.91 (m, 2H), 3.10 (m, 2H), 3.62 (m, 3H), 7.28 (m, 10H).

#### Example 115

Preparation of [S-[1R\*,2R\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-phenylmethyl]propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 115)



Compound 114 and Cbz-valine were reacted by a procedure analogous to that used for the synthesis of Compound 55 (DMF only as solvent) to give the title Compound 115.

mp 183-186°C.; [α]<sub>D</sub><sup>20</sup> = 38.7° (c 0.23, MeOH).

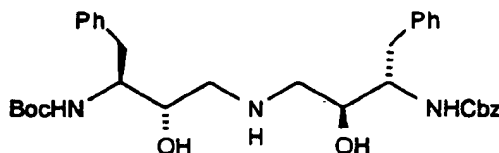
Mass Spec. FAB: M+H = 677.

Analysis calc. for C<sub>38</sub>H<sub>52</sub>N<sub>4</sub>O<sub>7</sub>·0.81 H<sub>2</sub>O:

	C, 66.01;	H, 7.82;	N, 8.10;
Found	C, 65.95;	H, 7.72;	N, 8.16.

#### Example 116

Preparation of [S-(R\*,R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl phenylmethyl ester (Compound 116)

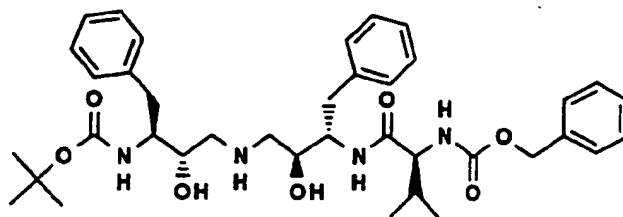


Compounds 27a and 113b (1 eq. of each) were reacted by a procedure analogous to that used for the synthesis of Compound 4b to give the title Compound 116 (white foam).

<sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 1.34 (s, 9H), 2.52 (m, 4H), 2.75 (m, 2H), 2.87 (m, 2H), 3.69 (m, 3H), 3.82 (m, 1H), 4.98 (s, 2H), 7.22 (m, 15H).

**Example 117**

Preparation of [S-(1R\*,2R\*(2R\*,3R\*))]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N'-[(phenylmethoxy)carbonyl]-L-valinamid (Compound 117)



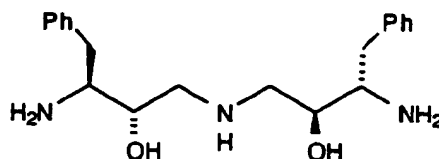
Compound 116 was converted to the title Compound 117 by a two-step procedure analogous to that used for the synthesis of Compound 115 (removal of the Cbz group using conditions analogous to those for Compound 7, and coupling of the resulting product with Cbz-valine analogous to Compound 55 [DMF only]). mp 170-175°C.;  $[\alpha]_D^{25} = -51.5^\circ$  (c 0.20, MeOH).

Mass Spec. FAB + ions: M+H= 677.

Analysis calc. for $C_{38}H_{52}N_4O_7 \cdot 0.59 H_2O$ :			
	C, 66.38;	H, 7.80;	N, 8.15;
Found	C, 66.25;	H, 7.61;	N, 8.28.

**Example 118**

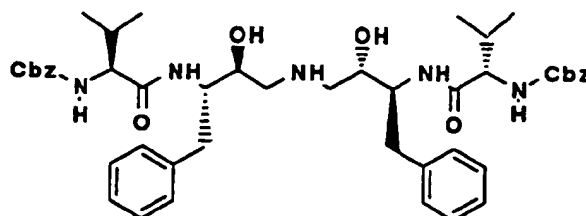
Preparation of [S-(R\*,R\*)]-1,1'-Iminobis(3-amino-4-phenyl-2-butanol) (Compound 118)



Compound 3 was converted to the title Compound 118 (which was used without further purification in the following Example as the tri-HCl salt) by a procedure analogous to that used for the synthesis of Compound 32.  $R_f = 0.035$  (20:2:78 MeOH:NH<sub>4</sub>OH:CHCl<sub>3</sub>).

**Example 119**

Preparation of [S-(1R\*,2R\*)]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[N'-[phenylmethoxy]carbonyl]-L-valinamide (Compound 119)



Compound 118 and Cbz-L-valin were reacted by a procedure analogous to that used for the synthesis

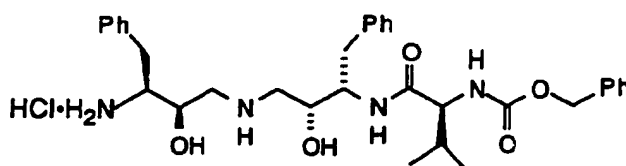
of Compound 75f to give the title Compound 119.  
 m.p. dec. 206-208°C;  $[\alpha]_D^{25} = -42.8^\circ$  (c 0.14, DMSO).  
 Ms: (FAB): 810 (M+H).

Anal. Calc. for  $C_{46}H_{59}N_5O_8 \cdot 1.08 H_2O$ :

	C, 66.62;	H, 7.43;	N, 8.44
Found:	C, 66.71;	H, 7.33;	N, 8.35

#### Example 120

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[(3-Amino-2-hydroxy-4-phenylbutyl)amino]-2-hydroxy-1-(phenylmethyl)-propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 120)

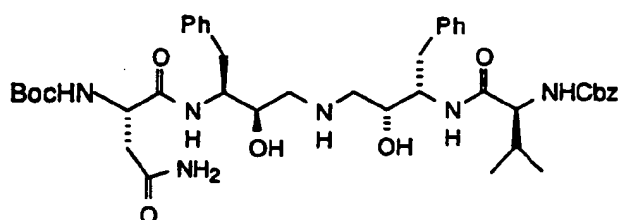


Compound 52 was converted to the title Compound 120 (used without further purification in the next Example) by a procedure analogous to that used for the synthesis of Compound 110.

<sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  0.52(d, J = 6.6 Hz, 3H), 0.56 (d, J = 6.6 Hz, 3H), 1.70 (m, 1H), 2.70 (m, 1H), 2.95 (m, 1H), 3.05 (m, 4H), 3.17 (m, 2H), 3.57 (d, J = 7.2 Hz, 1H), 3.72 (m, 1H), 3.80 (m, 1H), 4.07 (m, 1H), 4.28 (m, 1H), 5.11 (s, 2H), 7.12 - 7.42 (m's, 15H).

#### Example 121

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N<sup>2</sup>-[(1,1-Dimethylethoxy)carbonyl]-N-(2-hydroxy-3-[[2-hydroxy-4-phenyl-3-[[N-[(phenylmethoxy)carbonyl]-L-valyl]amino]butyl]amino]-1-(phenylmethyl)propyl]-L-asparaginamide (Compound 121)



Compound 120 was reacted with Boc-L-asparagine by a procedure analogous to that used for the synthesis of Compound 55 (DMF only; 2 eq. of N-methylmorpholine added) to give the title Compound 121.

mp 199 - 202°C;  $[\alpha]_D = -31^\circ$  (c 0.2, ACOH).

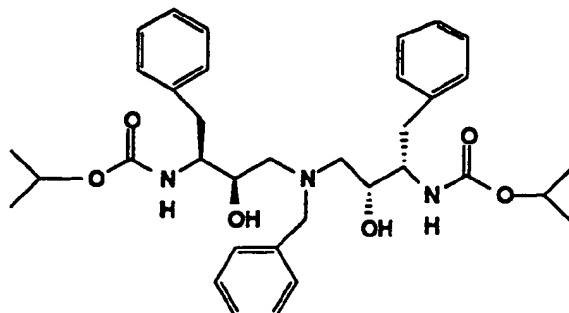
Mass Spec.: FAB (M + H)<sup>+</sup> 791.

Analysis calculated for  $C_{42}H_{58}N_6O_9 \cdot 0.61H_2O$ :

	C, 62.90;	H, 7.44;	N, 10.48;
Found:	C, 63.04;	H, 7.33;	N, 10.34.

## Example 122

Preparation of [R-(R\*,S\*)]-[[[(Phenylmethyl)imino]bis[2-hydroxy-1-(phenylmethyl)-3,1-propan diyl]biscarbamic acid, bis(1-methylethylester (Compound 122)

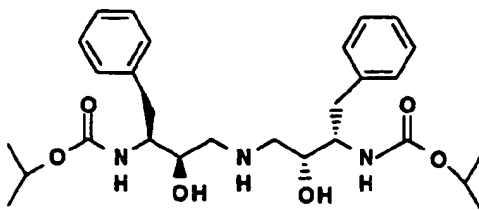


To a solution of Compound 32 (165 mg; 0.35 mmol) and 0.27 mL (1.56 mmol) of  $i\text{-Pr}_2\text{NEt}$  in 0.35 mL of dry DMF at  $0^\circ\text{C}$  was added 0.78 mL (0.78 mmol) of isopropyl chloroformate. The reaction mixture was stirred at RT for 72 h, at which point it was quenched with saturated aqueous  $\text{NaHCO}_3$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine and dried ( $\text{Na}_2\text{SO}_4$ ). The salts were filtered and the solvents removed *in vacuo* to give a residue, which was purified on silica gel (gradient of 75:25 to 50:50 hexane:EtOAc) to give 100 mg of Compound 122 (white solid).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.11 (d, 6H), 1.70 (1H), 1.17 (d, 6H), 2.50-2.59 (m, 4H), 2.70-2.83 (m, 4H), 3.40-3.51 (m, 2H), 3.60-3.83 (m, 5H), 4.69 (m, 2H), 4.76-4.82 (m, 2H), 7.13-7.35 (m, 15H).

## Example 123

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propandiy]biscarbamic acid, bis(1-methylethylester (Compound 123)



Compound 122 was converted to the title Compound 123 by a procedure analogous to that used for the synthesis of Compound 2.

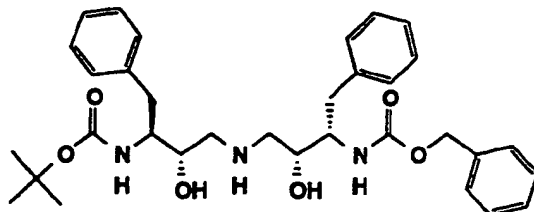
m.p.  $195 - 200^\circ\text{C}$ ;  $[\alpha]_D = -13.2^\circ$  (c, 0.09, MeOH)

Mass spec. (CI) (M+H) 516

Elemental Analysis (%) $\text{C}_{28}\text{H}_{41}\text{N}_3\text{O}_8 \cdot 0.63 \text{H}_2\text{O}$		
	Calc.	Found
C	65.22	64.00
H	8.01	7.88
N	8.15	7.80

**Example 124**

Preparation of [1S-[1R\*,2R\*(2S\*,3R\*)]]-[3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, phenylmethyl ester (Compound 124)

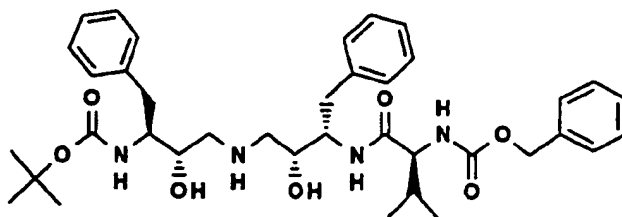


Compounds 27a and 44a (1 eq. of each) were reacted by a procedure analogous to that used for the synthesis of Compound 4b (white powder) to give the title Compound 124.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.30 (s, 9H), 2.57 (m, 6H), 2.80 (dd, J= 5.5, 13.5, 1H), 3.01 (d, J= 11 Hz, 1H), 3.41 (m, 1H), 3.50 (m, 1H), 3.60 (m, 1H), 3.70 (m, 1H), 4.73 (m, 1H), 4.85 (m, 1H), 4.88 (d, J= 13 Hz, 1H), 4.93 (d, J= 13 Hz, 2H), 6.40 (d, J= 9 Hz, 1H), 7.27 (m, 15H).

**Example 125**

Preparation of [S-[1R\*,2S\*(2R\*,3R\*)]-N-[3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[(phenylmethoxy)carbonyl]-L-valinamide (Compound 125)



Compound 124 was converted to the title Compound 125 by a two-step procedure analogous to that used for the synthesis of Compound 115 (removal of Cbz group using conditions analogous to those used for Compound 7 (AcOH used in place of MeOH), and coupling of the resulting product with Cbz-valine analogous to Compound 55 (DMF only).

mp 175-180°C; [α]<sub>D</sub><sup>20</sup> = -26.0° (c 0.15, MeOH).

Mass Spec. FAB + ions: M+H= 677.

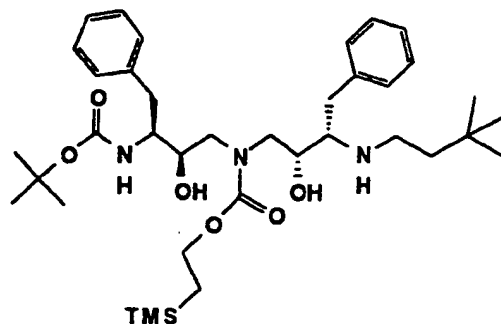
Analysis calc. for C<sub>38</sub>H<sub>52</sub>N<sub>4</sub>O<sub>7</sub>·0.95 H<sub>2</sub>O:

	C, 65.77;	H, 7.83;	N, 8.07;
Found	C, 65.55;	H, 7.59;	N, 8.29.

**Example 126**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[3-[(3,3-Dimethylbutyl)amino]-2-hydroxy-4-phenylbutyl]]2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 126)

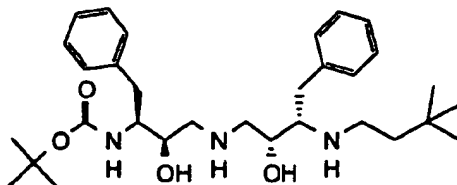




To a solution of Compound 48 (300 mg, 0.51 mmol) in 1.55 mL MeOH (adjusted to pH 6 with AcOH) was added 3,3-dimethylbutylaldehyde (70  $\mu$ L, 0.56 mmol, 1.1 eq.) and a small amount of pulverized 4Å molecular sieves. To this mixture at RT was added NaCNBH<sub>3</sub> (48 mg, 0.77 mmol) in two portions. The reaction was quenched after 2 h with 10 mL saturated NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered, concentrated, and dried *in vacuo* to yield 330 mg crude oil. The residue was purified by chromatography on a 3 x 16 cm silica gel column, eluting with CH<sub>2</sub>Cl<sub>2</sub>, then 98.9:1:0.1 and 97.8:2:0.2 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH to afford 238 mg (69%) of Compound 126. Mass Spec: 672 (M + H)<sup>+</sup>

#### Example 127

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[(3,3-Dimethylbutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 127)



Compound 126 was converted to the title Compound 127 by a procedure analogous to the one used for the synthesis of Compound 21.

mp 89-91°C; [ $\alpha$ ]<sub>D</sub> = +9° (c 0.24, MeOH).

Mass Spec: Fab (M + H)<sup>+</sup>: 528.

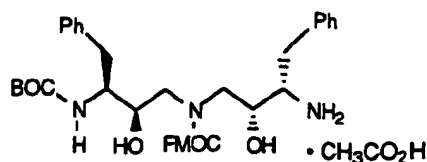
Analysis calculated for C<sub>31</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub>·0.74H<sub>2</sub>O:

	C, 68.82;	H, 9.40;	N, 7.77;
Found:	C, 68.57;	H, 9.16;	N, 8.02.

#### Example 128

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-Amino-2-hydroxy-4-phenylbutyl]](9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, monoacetate salt (Compound 128)

5



10 A solution of 1.69 g (2.1 mmoles) of Compound 107 and 2.0 ml of 1,4-cyclohexadiene in 60 ml of EtOH containing 225 mg of 10% Pd/C catalyst was stirred under a hydrogen atmosphere for 3.5 hr. The catalyst was removed by filtration through Celite and 0.5 ml of HOAc added. Evaporation to dryness gave 1.8 g (assumed 100% yield) of Compound 128 as a white solid. [TLC:  $R_f=0.38$ , 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub>]. Mass Spec. 666 (M+H).

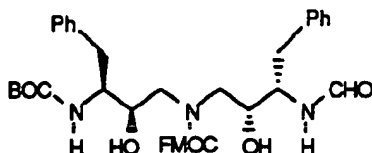
15

#### Example 129

16 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[(9H-Fluoren-9-ylmethoxy)carbonyl][3-(formylamino)-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 129)

20

25



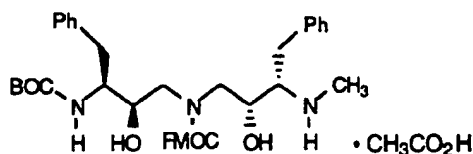
30 Formic acetic anhydride was prepared by the addition of 260  $\mu$ l of formic acid to 745  $\mu$ l of acetic anhydride at 0°C and the resulting solution then heated at 50°C for 2 h. The anhydride was dissolved in 5 ml of THF and added to a slurry of 1.8 g (assumed 2.1 mmoles) of Compound 128 in 20 ml of THF. The reaction was stirred at 0°C for 30 min, then at RT for 30 min, and then evaporated to dryness to yield the crude product as a white foam. This material was purified by flash chromatography on a 75 cc column of silica gel. Elution with 50% EtOAc-hexane, followed by 100% EtOAc gave 1.16 g (1.67 mmole, 80% yield over two steps) of Compound 129 as a solid white foam. [TLC:  $R_f=0.29$ , EtOAc] Mass Spec. 694 (M+H).

35

#### Example 130

40 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[(9H-Fluoren-9-ylmethoxy)carbonyl][2-hydroxy-3-(methylamino)-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, monoacetate salt (Compound 130)

45



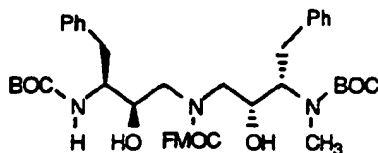
50

55 To a solution of 785 mg (1.13 mmoles) of Compound 129 in 10 ml of THF at 0°C was added dropwise 2.85 ml of 2 M borane-methyl sulfide in THF. After foaming ceased the reaction mixture was heated at 50°C for 1 h then cooled to 0°C and excess borane hydrolyzed by the dropwise addition of approx. 10 ml of MeOH. After reaction ceased, 0.5 ml of HOAc was added and the solution heated at 50°C for 6 h to destroy the amine-boron complex. The solution was evaporated to dryness and the residue purified by flash chromatography on a 35 cc column of silica gel (elution with 100% EtOAc, 10% MeOH-EtOAc, and 20% MeOH-EtOAc). After the appropriate fractions were combined, 0.5 ml of HOAc was added and the solvent removed to yield 625 mg (0.84 mmol, 75% yield) of Compound 130 as a solid white foam. This material contained approximately 3 equivalents of HOAc by <sup>1</sup>H NMR. [TLC:  $R_f=0.43$ , 10% MeOH-CH<sub>2</sub>Cl<sub>2</sub>].

Mass Spec. 690 (M+H).

#### Exempl 131

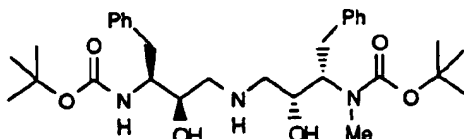
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]][(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]methylcarbamic acid, 1,1-dimethylethyl ester (Compound 131)



To a solution of 160 mg (0.166 mmole, based on 3 eq of HOAc) of Compound 130 and 137 mg (0.63 mmole) of di-*t*-butyl dicarbonate in 1 ml of DMF at 0°C was added, dropwise, 146 µl of Et<sub>3</sub>N. After 30 min an additional 65 mg of di-*t*-butyl dicarbonate and 75 µl of Et<sub>3</sub>N were added and stirring continued for an additional 30 min. The reaction was diluted with EtOAc and washed with water and brine, dried (MgSO<sub>4</sub>), and the solvent removed to yield a residue which was purified by flash chromatography on a 20 cc column of silica gel (elution with 25% EtOAc/hexane, followed by 50% EtOAc/hexane) to give 129 mg (0.166 mmole, 89% yield) of Compound 131 as a solid white foam. [TLC: R<sub>f</sub>=0.30, 50% EtOAc/Hexane] Mass Spec. 780 (M+H).

#### Example 132

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]]amino]-2-hydroxy-1-(phenylmethyl)propyl]methylcarbamic acid, 1,1-dimethylethyl ester (Compound 132)



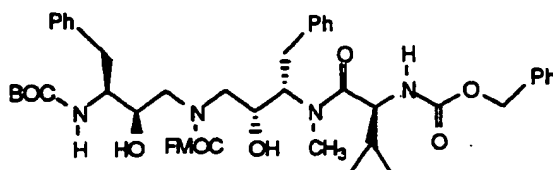
Compound 131 was converted to the title Compound 132 by a procedure analogous to the procedure used for the synthesis of Compound 42 (CH<sub>2</sub>Cl<sub>2</sub> used in place of DMF).

[α]<sub>D</sub><sup>20</sup> = -19.6° (c=0.6, MeOH); MS: (M+H)<sup>+</sup>=558; MW=557

Anal. Calc. for C<sub>31</sub>H<sub>47</sub>N<sub>3</sub>O<sub>8</sub> · 0.33 H<sub>2</sub>O: C, 66.06; H, 8.52; N, 7.46. Found: C, 66.00; H, 8.47; N, 7.52.

#### Example 133

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]][(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N-methyl-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-valinamide (Compound 133)

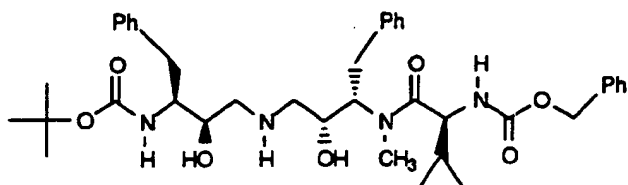


To a solution of 75 mg (0.087 mmol) of Compound 130 in 0.5 ml of MeOH was added a solution of 6.2 µl (0.087 mmole) of AcCl in 1 ml of MeOH. The solution was evaporated to dryness and the residue co-evaporated

from toluene to remove traces of HOAc. The residue was dried under high vacuum for 2 h to give 68 mg of the hydrochloride salt as a white solid. This material was diluted with 1 ml of CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0°C and 44 mg (0.174 mmol) of Cbz-L-valine and 49 mg (0.192 mmol) of BOP-Cl added as solids, followed by 46 µl (0.261 mmol) of i-Pr<sub>2</sub>NEt. The solution was stirred at 0°C for 4.5 hr and then placed directly on a 16 cc column of silica gel (elution with 50% EtOAc/hexane) to afford 70 mg (0.077 mmol, 88% yield) of the title Compound 133 as a white foam. [TLC: R<sub>f</sub>=0.27, 50% EtOAc-hexane].  
Mass Spec.: 913 (M+H).

#### Example 134

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N-methyl-N<sup>2</sup>[(phenylmethoxy)carbonyl]-L-valinamide (Compound 134)



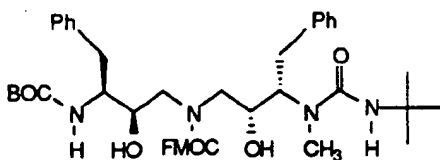
Compound 133 was converted to the title Compound 134 (solid white foam) by a procedure analogous to the procedure used for the synthesis of Compound 42 (CH<sub>2</sub>Cl<sub>2</sub> used in place of DMF). [α]<sub>D</sub> = -35.6° (c 0.82, MeOH).

Mass Spec.: 691 (M+H).

Elemental Analysis (%) for C <sub>39</sub> H <sub>54</sub> N <sub>4</sub> O <sub>7</sub> ·0.36 H <sub>2</sub> O			
	C; 67.18;	H; 7.91;	N; 8.03
Found:	C; 67.12;	H; 7.83;	N; 8.09

#### Example 135

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethyl)amino]carbonyl]methylamino]-2-hydroxy-4-phenylbutyl]][(9H-fluoren-9-ylmethoxy)carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 135)



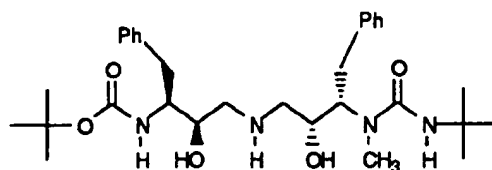
A solution of 110 mg of Compound 130 (0.13 mmol, material contained 3 eq. of HOAc by NMR) and 14.5 µl (0.16 mmol) of t-butyl isocyanate in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> was stirred at RT for 3 hr. An additional 7 µl of t-butyl isocyanate was added and stirring continued for 2.5 hr. The solution was evaporated to dryness to give 112 mg of a white foam which was combined with material from a similar reaction (total 130 mg) and purified by flash chromatography on a 20 cc column of silica gel (elution with 50% EtOAc/hexane) to afford 110 mg (0.14 mmol, 88% yield) of the title Compound 135 as a solid white foam. [TLC: R<sub>f</sub>=0.66, 100% EtOAc].

Mass Sp. c. 799 (M+H).

#### Example 136

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethyl)amino]carbonyl]methylamino]-2-hydroxy-

4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 136)



Compound 135 was converted to the title Compound 136 (solid white foam) by a procedure analogous to the procedure used for the synthesis of Compound 42 ( $\text{CH}_2\text{Cl}_2$  used in place of DMF). [TLC:  $R_f=0.31$ ,  $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$ , 90:10:1]

$[\alpha]_D^{20} = -15.2^\circ$  ( $c=0.27$ , MeOH)

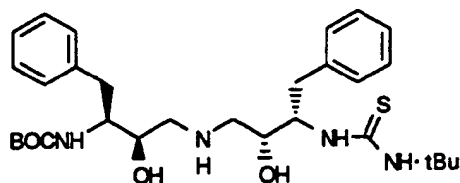
Mass Spec.: 557 (M+H).

Calc. for  $\text{C}_{31}\text{H}_{48}\text{N}_4\text{O}_5 \cdot 0.28 \text{ H}_2\text{O}$  (561.79): C, 66.28; H, 8.71, N, 9.97.

Found: C, 66.40; H, 8.59, N, 9.85.

#### Example 137

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethyl]amino]thioxomethyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 137)

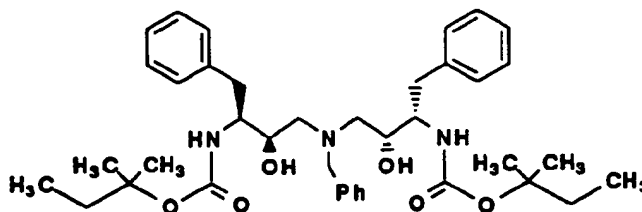


Compound 48 was converted to the title Compound 137 (white solid) by a two-step procedure analogous to that used for the preparation of Compound 50 (t-butylisothiocyanate used in place of t-butylisocyanate). m.p. 85 - 87°C ("softening" at 75 - 85°C).  $[\alpha]_D^{20} = -12.8^\circ$  ( $c=0.40$ , MeOH)

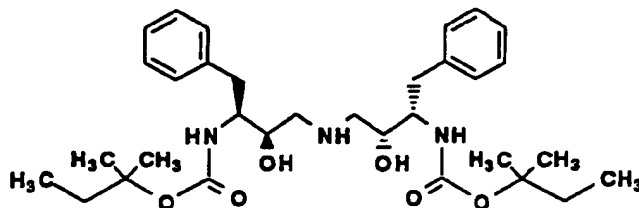
#### Compound 138

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, bis(1,1-dimethylpropyl)ester (Compound 138b)

##### (a) Compound 138a



Compound 138a was obtained as a white solid by reaction of Compound 32 with di-tert-amylidicarbonate using conditions analogous to those used for the synthesis of Compound 131 (i- $\text{Pr}_2\text{NEt}$  used instead of  $\text{Et}_3\text{N}$ ). Mass Spec. 662 (M+H)

(b) Compound 138b

Compound 138a was converted to Compound 138b (white solid) by a procedure analogous to that used for the preparation of Compound 2.

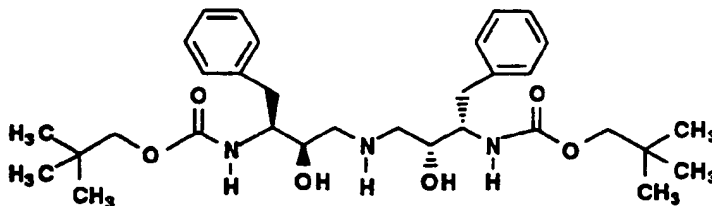
m.p. 161 - 163°C;  $[\alpha]_D^{20} = +1.47^\circ$  (c = 0.2, CH<sub>2</sub>Cl<sub>2</sub>)

Elemental Analysis  
(%) for C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>8</sub> ·  
0.52 H<sub>2</sub>O

	Calc.	Found
C	66.13	66.42
H	8.68	8.73
N	7.23	6.94

Example 139

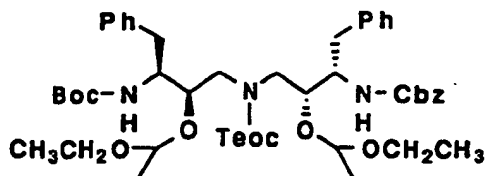
Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, bis (2,2-dimethylpropyl)ester (Compound 139)



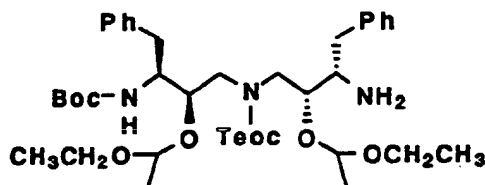
Compound 139 was obtained as a solid by reaction of Compound 32 with neopentyl chloroformate (J. Org. Chem. 49, 1174 (1984)), and subsequent deprotection analogous to the two step procedure used for the synthesis of Compound 123. m.p. 152 - 154°C;  $[\alpha]_D^{20} = -12.5^\circ$  (c = 0.1, CH<sub>3</sub>OH) TLC:R<sub>f</sub> = 0.43 (silica gel); Solvent:90:9:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH.

Example 140

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-(5,5-Dimethyl-2-oxo-3-oxazolidinyl)-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 140f)

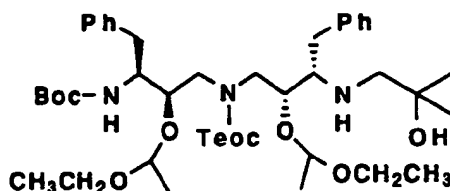
(a) Compound 140a

To a solution of the Cbz-intermediate formed during the first step of the synthesis of Compound 48 (100 mg, 0.138 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0^\circ\text{C}$  was added ethyl vinyl ether (300  $\mu\text{L}$ , 3.14 mmol), followed by pyridinium *p*-toluene sulfonate (10.7 mg, 0.042 mmol) and the reaction stirred at RT for 18 h. The reaction mixture was diluted with EtOAc and washed with saturated  $\text{NaHCO}_3$ . The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to yield a gummy white solid which was purified by silica gel chromatography, eluting with EtOAc (10 to 40%)/hexane to afford 105 mg of Compound 140a (88% yield) as a white residue. TLC (silica gel/ Hexanes:EtOAc 1:1):  $R_f = 0.7$

(b) Compound 140b

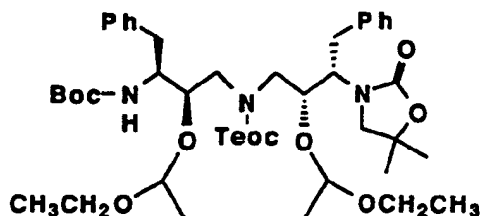
Compound 140a was converted to Compound 140b (colorless oil) by a procedure analogous to that used for the synthesis of Compound 54.

Mass Spec.: 732 (M+H)

(c) Compound 140c

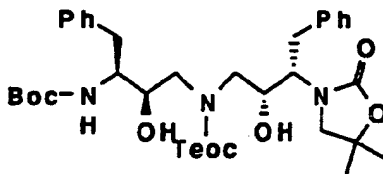
To a solution of Compound 140b (175 mg, 0.24 mol) in EtOH (2 mL) in a pressure tube was added isobutylene oxide (0.66 mL, 7.17 mmol) and the tube sealed under argon and heated at  $110^\circ\text{C}$  for 4 h, and then at  $150^\circ\text{C}$  for 2 h. The solvents were removed *in vacuo*, and the oily residue purified by silica gel chromatography, eluting with  $\text{CH}_3\text{OH}$  (1 to 10%)/ $\text{CHCl}_3$  to give 138 mg of Compound 140c (71% yield) as a colorless gummy residue.

Mass Spec. 805 (M+H)

(d) Compound 140d

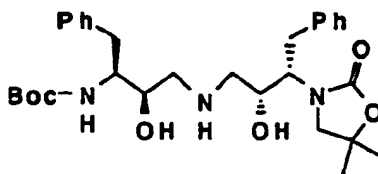
To a solution of Compound 140c (103 mg, 0.13 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (375  $\mu\text{L}$ ) at  $0^\circ\text{C}$  was added pyridine (125  $\mu\text{L}$ , 1.54 mmol), followed by 20%  $\text{COCl}_2$  in toluene (166  $\mu\text{L}$ , 1.93 M) and the mixture stirred at  $0^\circ\text{C}$  for 25 min. The reaction mixture was quenched with saturated  $\text{NaHCO}_3$ , extracted with EtOAc, the organic phase dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford 98 mg of Compound 140d (ca. 91% crude yield) as yellow foamy residue.

TLC (silica gel/ $\text{CHCl}_3$ :MeOH 98:2):  $R_f = 0.26$

(e) Compound 140e

To a solution of Compound 140d (98 mg, 0.12 mmol) in 1.5 mL acetone was added pyridinium *p*-toluene sulfonate (98 mg, 0.12 mmol) and the yellow solution stirred at RT for 18 h. The solvent was removed and the residue taken into EtOAc (10 mL) and washed with saturated  $\text{NaHCO}_3$ . The organic extracts were dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to dryness. The crude product was purified by silica gel chromatography, eluting with  $\text{CH}_3\text{OH}$  (1 to 10%)/ $\text{CHCl}_3$  to afford 68 mg of Compound 140e (81% yield) as a yellow residue.

Mass Spec. 686 (M+H)

(f) Compound 140f

Compound 140e was converted to the title Compound 140f (yellow solid) by a procedure analogous to that used for the synthesis of Compound 21.

m.p.  $55-58^\circ\text{C}$ ,  $[\alpha]_D = -3.96^\circ$  ( $c = 0.2$ ,  $\text{CH}_2\text{Cl}_2$ ).

Analysis for:  $\text{C}_{30}\text{H}_{43}\text{N}_3\text{O}_8 \cdot 2.19 \text{H}_2\text{O}$

Calculated: C, 62.00; H, 8.22; N, 7.23;

Found: C, 62.25; H, 7.63; N, 6.98.

## Exmpl 141

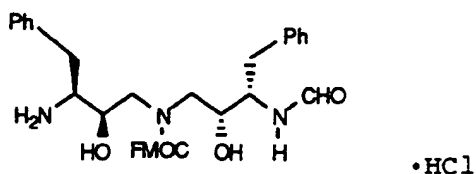
Pr paration f [S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]methylamino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N²-[(phenylmethoxy)carbonyl]-L-valinamid] (Compound 141)



(a) Compound 141a

5

10

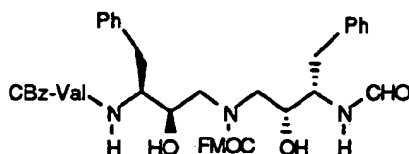


Compound 129 was converted to Compound 141a (yellow solid) by a procedure analogous to that used for the synthesis of Compound 32.

15

(b) Compound 141b

20

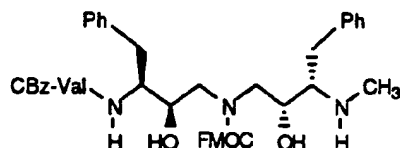


25

Compound 141a was converted to Compound 141b (white solid) by a procedure analogous to that used for the synthesis of Compound 51 ( $\text{CH}_2\text{Cl}_2$  was used as solvent). TLC:  $R_f=0.21$ , 100% EtOAc.

(c) Compound 141c

30



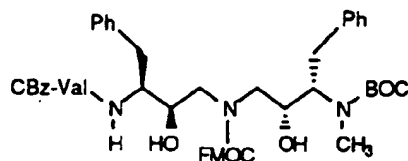
35

Compound 141b was converted to Compound 141c (white foam) by a procedure analogous to that used for the synthesis of Compound 130. TLC:  $R_f=0.42$ ,  $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$ , 90:10:1.

40

(d) Compound 141d

45

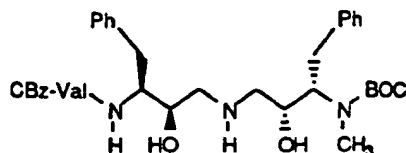


50

Compound 141c was converted to Compound 141d (white foam) by a procedure analogous to that used for the synthesis of Compound 131.

55

## (e) Compound 141



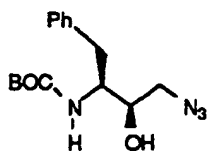
Compound 141d was converted to Compound 141e (white foam) by a procedure analogous to that used for the synthesis of Compound 42. TLC:  $R_f = 0.38$ ,  $\text{CH}_2\text{Cl}_2\text{:MeOH:NH}_4\text{OH}$ , 90:10:0.1 (UV detection).  $[\alpha]_D = -27.9^\circ$  (c 0.72, MeOH)

Elemental Analysis (%) $\text{C}_{39}\text{H}_{54}\text{N}_4\text{O}_7$		
	Calc.	Found
C	67.80	67.51
H	7.88	7.94
N	8.11	8.14

## Example 142

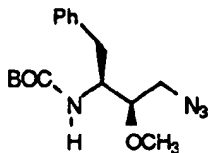
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-methoxy-1-(phenylmethyl)propyl]carbamic acid 1,1-dimethylethyl ester (Compound 142d)

## (a) Compound 142a



A solution of 300 mg (1.14 mmole) of Compound 1b(i), 186 mg (2.85 mmoles) of  $\text{NaN}_3$  and 111 mg (2.05 mmoles) of  $\text{NH}_4\text{Cl}$  in 6 ml of MeOH was stirred at reflux overnight. The white solid residue obtained on removal of solvent was dissolved in EtOAc and washed with  $\text{H}_2\text{O}$  and brine. Drying ( $\text{MgSO}_4$ ) and concentration gave 300 mg (0.98 mmole, 86%) of Compound 142a as a white solid. TLC:  $R_f = 0.21$ , 25% EtOAc-hexane.

## (b) Compound 142b

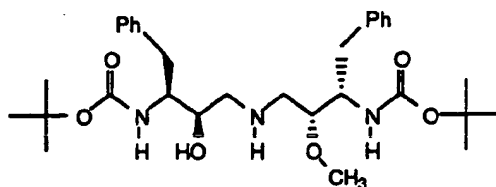


To a suspension of 48 mg (1.2 mmoles) of 60% NaH (hexane washed) in 1 ml of dry THF at RT was added a solution of 295 mg (0.96 mmole) of Compound 142a in 4 ml of THF. The reaction was stirred for 2 hr at which time 89  $\mu\text{l}$  (1.44 moles) of methyl iodide was added. Stirring was continued for 1 hr then the reaction was diluted with EtOAc and washed with  $\text{H}_2\text{O}$ , 10%  $\text{Na}_2\text{S}_2\text{O}_3$ , and brine. After drying ( $\text{MgSO}_4$ ), removal of solvent gave a white solid residue which was purified by flash chromatography on a 130 cc column of silica gel (elution with 20% EtOAc/hexane) to give 206 mg (0.64 mmole, 67%) of Compound 142b as a white solid. TLC:  $R_f = 0.55$ ,

25% EtOAc-hexan .

(c) Compound 142c

A solution of 150 mg (0.47 mmole) of Compound 142b in 3 ml of MeOH containing 45 mg of 10% Pd/C was hydrogenated at RT for 1.5 hr (balloon). The reaction was diluted with additional MeOH, 0.5 ml of NH<sub>4</sub>OH was added, and stirring was continued for 15 min. The catalyst was removed by filtration through Celite (MeOH wash) and the filtrate concentrated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>), and the solvent evaporated to afford 122 mg (0.41 mmole, 88%) of Compound 142c as a white solid. TLC: R<sub>f</sub>=0.28, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, (90:10:1).

(d) Compound 142d

Compounds 142c and 1b(i) were reacted by a procedure analogous to that used for the synthesis of Compound 4b to give the title Compound 142d (white foam). TLC: R<sub>f</sub> = 0.37, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:10:0.1 [α]<sub>D</sub> = -3.9° (c 0.67, MeOH)

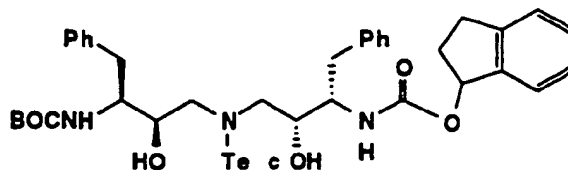
## Elemental Analysis (%)

C<sub>31</sub>H<sub>47</sub>N<sub>3</sub>O<sub>6</sub> • 0.78 H<sub>2</sub>O

	Calc.	Found
C	65.11	64.75
H	8.56	8.22
N	7.35	7.71

Example 143

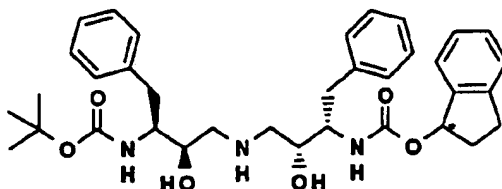
Preparation of [1S-[1R\*,2S\*)]-[2-(Trimethylsilyl)ethoxy]carbonyl]imino]bis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 2,3-dihydro-1H-inden-1-yl ester (Compound 143)



A solution of 53 mg (0.0924 mmol) of Compound 48 in 200  $\mu$ L of  $\text{CH}_3\text{CN}$  at RT were added 29 mg of Compound 67a and 26  $\mu$ L of  $\text{Et}_3\text{N}$ . After 22 h, an additional 3 mg of Compound 67a and 5  $\mu$ L of  $\text{Et}_3\text{N}$  were added to the reaction mixture. After 48 h, the mixture was diluted with 50 mL of  $\text{CH}_2\text{Cl}_2$  and washed with 10% citric acid and saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. Flash chromatography on silica gel eluting with 10-50% EtOAc-hexane provided 57 mg (84%) of Compound 143.

#### Example 144

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]-bis(carbamic acid), 1,1-dimethylethyl-2,3-dihydro-1H-inden-1-yl ester (Compound 144)

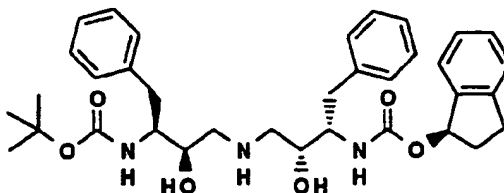


Compound 143 was converted to the title Compound 144 by a procedure analogous to that used for the synthesis of Compound 21. (1:1 mixture R:S at \*)  
mp 157-166°C;  $[\alpha]_D^{20} = -11^\circ$  (c=0.35,  $\text{CH}_3\text{OH}$ )  
Mass Spec. 604 (M+H)<sup>+</sup>

Elemental Analysis (%) $\text{C}_{35}\text{H}_{45}\text{N}_3\text{O}_6 \cdot 0.71 \text{H}_2\text{O}$		
	Calc.	Found
C	68.18	68.40
H	7.59	7.55
N	6.81	6.59

#### Example 145

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl(R)-2,3-dihydro-1H-inden-1-ylester (Compound 145)



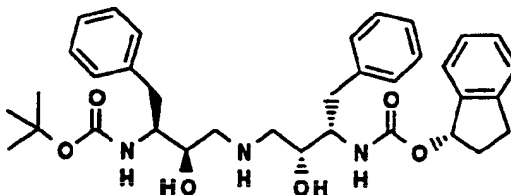
Compound 48 was converted to the title Compound 145 by a two-step procedure analogous to that used for the synthesis of Compound 144 except that the p-nitrophenyl carbonate of R-(-)-indanol was used.  
mp 187-190°C;  $[\alpha]_D^{20} = -4.9^\circ$  (c=0.35, DMSO)  
Mass Spec. 604 (M+H)<sup>+</sup>

El mental Analysis  
(%)  $C_{35}H_{45}N_3O_6 + 0.51$   
 $H_2O$

	Calc.	Found
C	68.58	68.24
H	7.57	7.29
N	6.86	7.20

#### Example 146

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl(S)-2,3-dihydro-1H-inden-1-yl ester (Compound 146)



Compound 48 was converted to the title Compound 146 by a two-step procedure analogous to that used for the synthesis of Compound 144 except that the p-nitrophenyl carbonate of S-(+)-indanol was used.  
mp 175-178°C;  $[\alpha]^{20}_D = -26^\circ$  (c=0.12,  $CH_3OH$ )  
Mass Spec. 604 (M+H)<sup>+</sup>

#### Elemental Analysis (%)

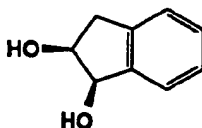
$C_{35}H_{45}N_3O_6 \cdot 0.25 H_2O$

	Calc.	Found
C	69.12	68.96
H	7.54	7.62
N	6.91	7.07

#### Example 147

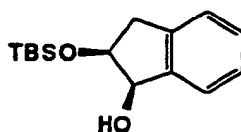
Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2,3-dihydro-2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1H-inden-1-yl ester, 1:1 mixture of 1R,2R- and 1S,2S-diastereomers on indane ring (Compound 147d)

##### (a) Compound 147a



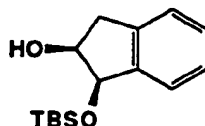
To a solution of 200 mg of  $\text{OsO}_4$  in 100 mL of dry  $\text{CH}_2\text{Cl}_2$  were added 14.6 g (125 mmol) of N-methylmorpholine oxide and 15.2 g (125 mmol) of phenylboronic acid. To the resulting solution was added a solution of 11.6 g of indene in 200 mL of  $\text{CH}_2\text{Cl}_2$  over 10 min. The resulting orange solution was stirred at RT for 45 min and the reaction quenched with 10% sodium thiosulfate (RT, 1 hr). The mixture was diluted with EtOAc, washed with brine and the organic layer dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to give 27 g of a phenylboronate intermediate. The solid was dissolved in 250 mL of THF and 300 mL of 2N NaOH was added. The mixture was cooled to 0°C and treated dropwise with 200 mL of 30%  $\text{H}_2\text{O}_2$ . The mixture was stirred at RT for 2 h and at 50°C for 1 h. After cooling to RT, the aqueous layer was saturated with NaCl, diluted with 500 mL of EtOAc and the organic layer separated and concentrated *in vacuo*. The aqueous layer was extracted with EtOAc and the combined organics washed with brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give 13.3 g of a residue. Flash chromatography of the residue on silica gel, eluting with 10-100% EtOAc-hexane, provided 6.64 g (44%) of Compound 147a.

(b) Compound 147b(i)



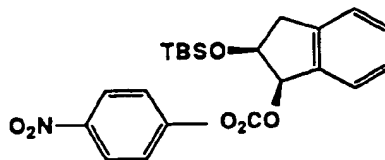
and

Compound 147b(ii)

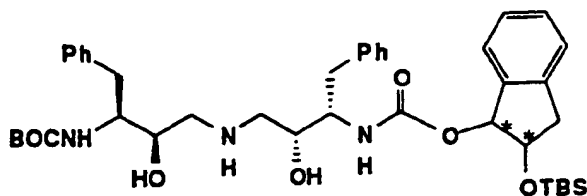


To a solution of the diol Compound 147a in 70 mL of DMF were added 6.4 g (42 mmol) of t-butyldimethylsilyl chloride and 3.6 g (53 mmol) of imidazole. The mixture, containing Compounds 147b(i) and 147b(ii), was stirred at RT for 24 h and the solvent removed *in vacuo*. The residue was taken up in Et<sub>2</sub>O and washed with saturated  $\text{NaHCO}_3$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* to give 9.27 g of a colorless oil. Flash chromatography on silica gel, eluting with 0-10% Et<sub>2</sub>O-hexane, provided 1.38 g (26%) of Compound 147b(i) as a colorless oil.

(c) Compound 147c



Compound 147b(i) was converted to Compound 147c by a procedure analogous to that used for the synthesis of Compound 67a [pyridine was used as base and co-solvent (3:1  $\text{CH}_2\text{Cl}_2$ /pyridine)].

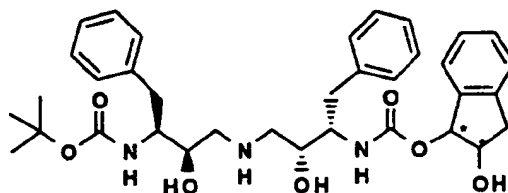
(d) Compound 147d

(1:1 mixture at \*; R,S :S,R)

To a solution of 211 mg (0.476 mmol) of Compound 54 in 2 mL DMF at RT were added 0.26 mL of *i*-Pr<sub>2</sub>NEt and then a solution of 225 mg (0.523 mmol) of Compound 147c in 2 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at RT for 72 h then diluted with EtOAc and washed with 0.1N NaOH and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give 381 mg of crude material. Flash chromatography on silica gel, eluting with 95:5:0.25 CHCl<sub>3</sub>/CH<sub>3</sub>OH/NH<sub>4</sub>OH, provided 144 mg (41%) of the title Compound 147d.

## Example 148

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2,3-dihydro-2-hydroxy-1H-inden-1-yl ester (Compound 148)



\*1:1 Mixture of diastereomers (R,S:S,R)

To a solution of 143 mg (0.195 mmol) of Compound 147d in 1.0 mL of dry THF at 0°C was added 5 mL of a cold (0°C) HF-pyridine solution (prepared by adding 1 mL of HF-pyridine to an ice cold solution of 2 mL pyridine in 7 mL of dry THF). The resulting solution was stirred at 0°C for 2 h and at RT for 2 h. The mixture was diluted with CHCl<sub>3</sub> and washed with saturated NaHCO<sub>3</sub> and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give 123 mg (~100%) of the title Compound 148. The compound was triturated with Et<sub>2</sub>O and lyophilized from dioxane.

mp 135-140°C (soft at 75°C); [α]<sub>D</sub><sup>20</sup> = -3° (c 0.20, CH<sub>3</sub>OH)Mass Spec. 620 (M+H)<sup>+</sup>

Elemental Analysis (%) C <sub>35</sub> H <sub>45</sub> N <sub>3</sub> O <sub>7</sub> ·0.054 H <sub>2</sub> O		
	Calc.	Found
C	66.78	66.86
H	7.38	7.28
N	6.67	6.59

## Example 149

Preparation of [1S-(1R\*, 2S\*)]-[[[2-(Trimethylsilyl)ethoxy]carbonyl]imino]bis-[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-4-[(phenylmethoxy)carbonyl]amino]butyl

est r (Compound 149 )

(a) Compound 149a



Compound 149a was prepared from 4-aminobutyric acid using a procedure analogous to that used for the synthesis of Compound 85a.

(b) Compound 149b



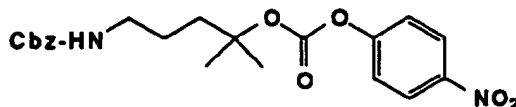
Thionyl chloride (2.91 ml; 40 mmol) was added dropwise to a solution of Compound 149a (4.74 g; 20 mmol) in 65 ml of MeOH at -20°C. After warming to RT, the reaction mixture was stirred for 18 hr then diluted with Et<sub>2</sub>O and the resulting organic layer washed with saturated NaHCO<sub>3</sub> and brine. After drying over MgSO<sub>4</sub>, the organic layer was concentrated to afford 4.475 g (89%) of crude Compound 149b as a colorless oil. A 3.5 g portion of this material was chromatographed on a 5 x 15 cm silica gel column using hexane:EtOAc, 85:15 and hexane:EtOAc, 75:25 as the mobile phase to afford 3.28 g (84% yield) of Compound 149b as a colorless liquid.

(c) Compound 149c



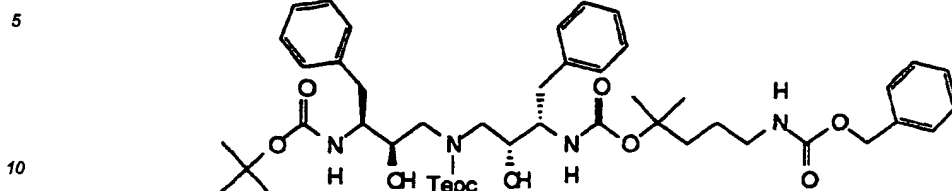
A solution of Compound 149b (500 mg; 2 mmol) in 4 ml of THF was added to a solution of MeLi (5.7 ml 1.4 M in Et<sub>2</sub>O; 8 mmol) in 6 ml of THF at -78°C. After stirring 5 h at -78°C, the reaction mixture was quenched with saturated NH<sub>4</sub>Cl and the resulting mixture extracted with Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and brine. After drying over MgSO<sub>4</sub>, the organic layer was concentrated and the resulting liquid purified on a 2.5 x 25 cm silica gel column using hexane:EtOAc, 6:4 as the mobile phase to afford 294 mg (59%) of Compound 149c as a colorless liquid.

(d) Compound 149d



4-Nitrophenylchloroformate (350 mg; 1.70 mmol) in 1 ml of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise to a solution of Compound 149c (280 mg; 1.11 mmol) in 2.5 ml of CH<sub>2</sub>Cl<sub>2</sub> and 0.5 ml pyridine. After stirring for 2 h at 0°C, an additional 0.25 ml of pyridine and 4-nitrophenylchloroformate (225 mg; 1.10 mmol) were added. The reaction mixture was stirred an additional 2 h at 0°C after which time 75 ml of Et<sub>2</sub>O was added. The organic layer was washed with H<sub>2</sub>O, 0.1N NaOH, H<sub>2</sub>O, 5% cupric sulfate solution, H<sub>2</sub>O, and brine. Drying (MgSO<sub>4</sub>) and concentration afforded a solid residue which was purified on a 2.5 x 20 cm silica gel column using hexane:EtOAc, 75:25 to afford 370 mg (80%) of Compound 149d as a light yellow oil.



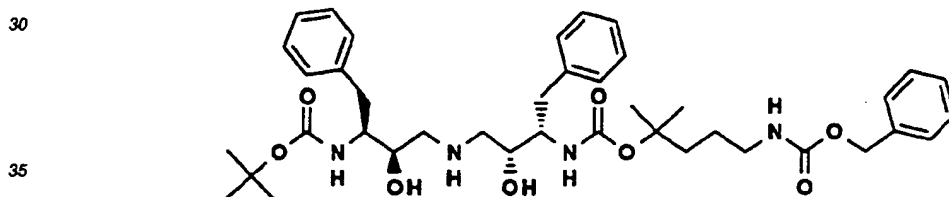
( ) Compound 149e

A mixture of Compound 48 (447 mg; 0.76 mmol), Compound 149d (357 mg; 0.84 mmol) and *i*-Pr<sub>2</sub>NEt (0.29 ml; 1.70 mmol) in 1.5 ml of CH<sub>3</sub>CN was stirred 72 h at RT. An additional quantity of *i*-Pr<sub>2</sub>NEt (0.15 ml; 0.86 mmol) was added and the reaction mixture was heated to 45°C for 18 h. The volatiles were removed *in vacuo* and the residue was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O, 0.1N NaOH, H<sub>2</sub>O, saturated aq. KHSO<sub>4</sub>, H<sub>2</sub>O, and brine. Drying (MgSO<sub>4</sub>) and concentration afforded a residue which was purified on a 2.5 x 15 cm silica gel column using 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 540 mg (82%) of Compound 149e as a white foamy solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>; 70°C): δ 0.01 (s, 9H) 0.93 (t, J = 8, 8.5 Hz, 2H), 1.19 (s, 6H), 1.23 (s, 9H), 1.32 (m, 2H), 1.53 (m, 2H), 2.56 (m, 2H), 3.15 (m, 2H), 3.57 (m, 4H), 3.68 (m, 2H), 4.07 (m, 2H), 4.79 (m, 2H), 5.00 (s, 2H), 6.27 (brs, 2H), 6.90 (brs, 1H), 7.11 (m, 2H), 7.18 (m, 8H), 7.31 (m, 5H).

Example 150

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-4-[[[(phenylmethoxy)carbonyl]amino]butyl ester (Compound 150)



Compound 149e was converted to the title Compound 150 (white solid) by a procedure analogous to that of Example 21.

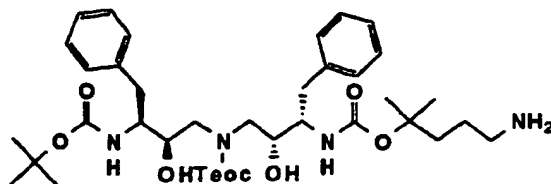
mp 153-155°C; [α]<sub>D</sub><sup>25</sup> = -18.0° (c 0.10, MeOH).

Mass Spec. FAB+ ion: (M+H) = 721.

Analysis calc. for C <sub>40</sub> H <sub>56</sub> N <sub>4</sub> O <sub>8</sub> :			
	C, 66.64;	H, 7.83;	N, 7.77;
Found:	C, 66.36;	H, 7.81;	N, 7.75.

Example 151

Preparation of [1S-(1R\*,2S\*)]-[[[2-(Trimethylsilyl)ethoxy]carbonyl]imino]-bis[[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 4-amino-1,1-dimethylbutyl ester (Compound 151)

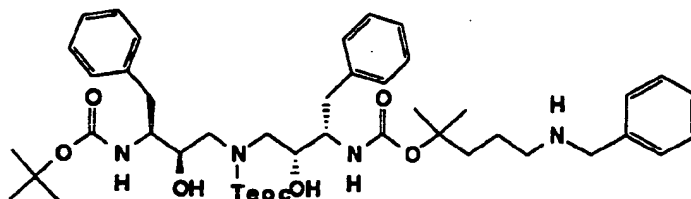


Compound 149e was converted to the title Compound 151 (colorless oil) using conditions analogous to those used for the synthesis of Compound 7.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ;  $70^\circ\text{C}$ ):  $\delta$  0.01 (s, 9H), 0.93 (t,  $J = 9, 8$  Hz, 2H), 1.20 (s, 6H), 1.22 (m; buried under large singlets, 2H), 1.23 (s, 9H), 2.43 (m, 2H), 2.55 (m, 2H), 2.93 (dd,  $J = 3.5, 14$  Hz, 2H), 3.05 (m, 4H), 3.53 (m, 4H), 3.65 (m, 2H), 4.02 (m, 2H), 6.23 (brs, 2H), 7.12 (m, 10H).

#### Example 152

Preparation of [1S-(1R\*,2S\*)]-[[[2-(Trimethylsilyl)ethoxy]carbonyl]imino]-bis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-4-[(phenylmethyl)amino]butyl ester (Compound 152)

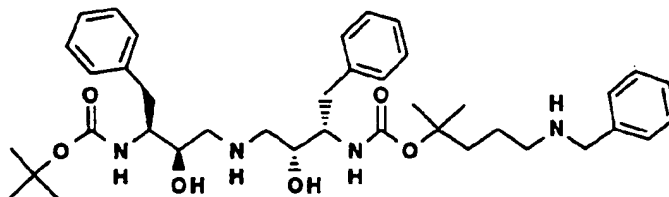


$\text{NaBH}(\text{OAc})_3$  (57 mg; 0.26 mmol) was added to a solution of Compound 151 (125 mg; 0.178 mmol) and benzaldehyde (18  $\mu\text{l}$ ; 0.178 mmol) in 1,2-dichloroethane at RT. After stirring for 3 h the solvent was removed *in vacuo* and the residue was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$  and concentrated to afford a crude residue which was purified on a 2.5 x 8 cm silica gel column, using  $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$ , 94.5:5.0:0.5 to give 125 mg (86%) of the title Compound 152 as a white foam.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ;  $70^\circ\text{C}$ ):  $\delta$  0.01 (s, 9H), 0.93 (t,  $J = 9, 8$  Hz, 2H), 1.21 (s, 6H), 1.23 (s, 9H), 1.33 (m, 2H), 1.58 (m, 2H), 2.48 (m, 2H), 2.57 (m, 2H), 2.94 (dd,  $J = 3, 14$  Hz, 2H), 3.15 (m, 2H), 3.54 (m, 4H), 3.68 (m, 2H), 3.72 (s, 2H), 4.05 (m, 2H), 4.80 (m, 2H), 6.26 (brs, 2H), 7.17 (m, 10H), 7.30 (m, 5H).

#### Example 153

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-4-[(phenylmethyl)amino]butyl ester (Compound 153)



Compound 152 was converted to the title Compound 153 (white solid) by a procedure analogous to that used for the synthesis of Compound 21.

mp  $128-132^\circ\text{C}$ ;  $[\alpha]_D = -4.8^\circ$  (c 0.42, MeOH).

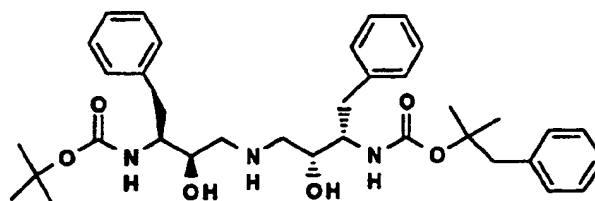
Mass Spec. FAB + ion:  $(\text{M}+\text{H}) = 677$ .

Analysis calc. for  $C_{39}H_{56}N_4O_8 \cdot 0.52 H_2O$ :

	C, 68.27;	H, 8.38;	N, 8.16;
Found:	C, 68.14;	H, 8.25;	N, 8.29.

**Example 154**

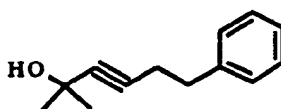
Preparation of [R-(R\*,S\*)]-Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-2-phenylethyl ester (Compound 154)



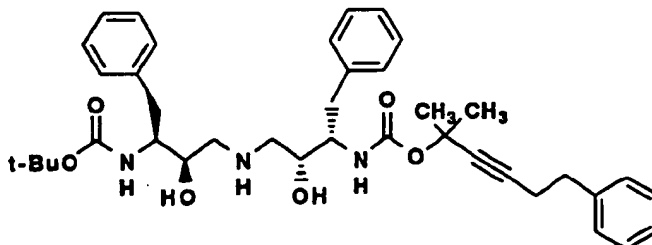
$\alpha,\alpha$ -Dimethylphenethyl alcohol was converted to the title Compound 154 (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 ( $Et_3N$  and DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).  
m.p. 161 - 164°C

**Example 155**

[1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-5-phenyl-2-pentynyl ester (Compound 155b)]

**(a) Compound 155a**

To a -78°C solution of 4-phenyl-1-butyne (1.00 g, 7.68 mmol) in THF (4.40 mL) was added dropwise a solution of n-BuLi/hexane (3.24 mL of a 2.49 M solution) and the resulting solution stirred at -78°C for 1 h. A solution of acetone (0.59 mL, 8.07 mmol) in THF (1.0 mL) was added dropwise at -78°C and the resulting solution stirred at -78°C for 3 h at which point a solution of aqueous  $NH_4Cl$  (9 mL of a 1 M solution) was added. The aqueous layer was extracted with EtOAc and the combined organic extracts dried (anhydrous  $Na_2SO_4$ ) and concentrated in vacuo to give a yellow oil. This crude material was chromatographed on silica gel (100 mL) eluting with 10:1 hexane:EtOAc to give Compound 155a (1.36 g, 94%) as a clear colorless oil.

**(b) Compound 155b**

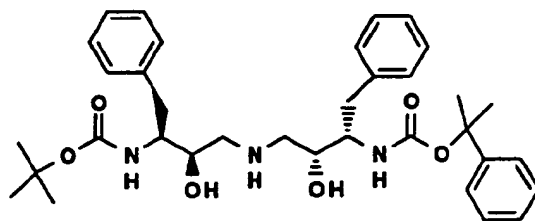
Compound 155a was converted to the title Compound 155b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

m.p. 140° - 142°C;  $\alpha_D = +2.0^\circ$  (c = 0.2, MeOH)

Elemental Analysis (%) for $C_{39}H_{51}N_3O_8 \cdot 0.87 H_2O$		
	Calc.	Found
C	69.55	69.40
H	7.89	7.73
N	6.24	6.39

#### Example 156

Preparation of [1S-(1R\*,2S\*)]-2-hydroxy-1-(phenylmethyl)-3,1-propanediyl)biscarbamic acid, 1,1-dimethylethyl-1-methyl-1-phenylethyl ester (Compound 156)



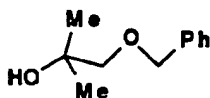
Dimethylphenyl carbinol was converted to the title Compound 156 (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 ( $Et_3N$  and DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

m.p. 89 - 92°C

#### Example 157

Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl)]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-2-(phenylmethoxy)ethyl ester (Compound 157b)

##### (a) Compound 157a

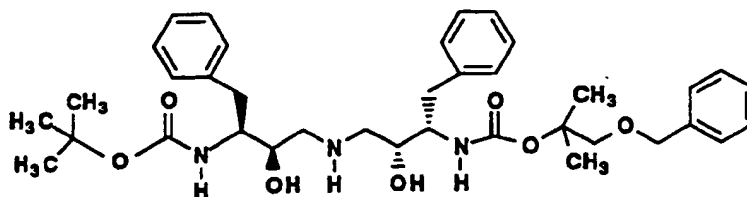


Compound 157a was prepared from benzyloxyacetyl chloride by a procedure analogous to that used for the synthesis of Compound 149c.

(b) Compound 157b

5

10



15

Compound 157a was converted to the title Compound 157b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

m.p. 129 - 135°C;  $[\alpha]^{20}_D = -3.5^\circ$  (c 0.5, CH<sub>3</sub>OH)

20

Elemental Analysis  
(%) Calculated for  
C<sub>37</sub>H<sub>51</sub>N<sub>3</sub>O<sub>7</sub> · 1.37 H<sub>2</sub>O

25

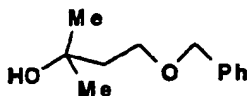
	Calc.	Found
C	65.89	65.52
H	8.03	7.64
N	6.23	6.60

30 Example 158

Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-3-(phenylmethoxy)propyl ester (Compound 158b)

35 (a) Compound 158a

40



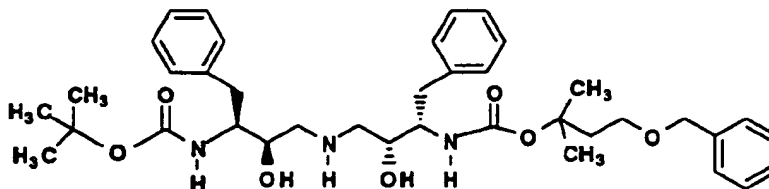
45

To a solution of 3M MeMgCl in THF (5 mL, 15 mmol) at -20°C was added 5 mL of THF and a solution of 4-benzyloxy-2-butanone (1.735 mL, 10 mmol) in 5 mL of THF. After the addition was complete, the reaction mixture was warmed to RT and quenched with 10 mL of water. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the organic phase was separated, dried (MgSO<sub>4</sub>) and concentrated to provide the Compound 158a (1.8 g, 92%) as a colorless oil.

(b) Compound 158b

50

55



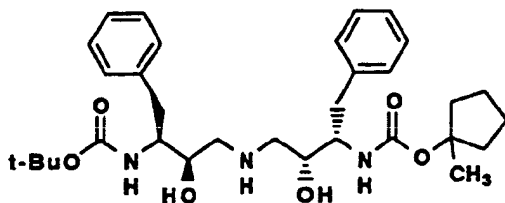
Compound 158a was converted to the title Compound 158b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (Et<sub>3</sub>N and DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

pling of the p-nitrophenyl carbonate to Compound 48).  
 m.p. 122 - 125°C;  $[\alpha]_D^{20} = -4.8^\circ$  (c=0.5, CH<sub>3</sub>OH)

Elemental Analysis (%) Calculated for C <sub>38</sub> H <sub>53</sub> N <sub>3</sub> O <sub>7</sub> · 1.30 H <sub>2</sub> O		
	Calc.	Found
C	66.41	66.58
H	8.15	7.89
N	6.11	5.94

### Example 159

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl 1-methylcyclopentyl ester (Compound 159)

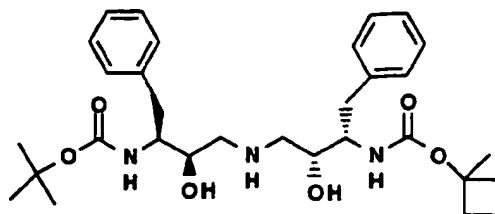


1-Methyl-1-cyclopentanol was converted to the title Compound 159 by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).  
 m.p. 160 - 162°C;  $[\alpha]_D = -4.3^\circ$  (c 0.21)

Elemental Analysis (%) for C <sub>32</sub> H <sub>47</sub> N <sub>3</sub> O <sub>6</sub> · 1.54 H <sub>2</sub> O		
	Calc.	Found
C	64.34	64.15
H	8.45	8.03
N	7.03	7.22

### Example 160

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl-1-methylcyclobutyl ester (Compound 160)



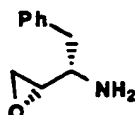
1-Methyl-1-cyclobutanol was converted to the title Compound 160 (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 ( $\text{Et}_3\text{N}$  and DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).  
m.p. 179 - 182°C

Elemental Analysis (%) $\text{C}_{31}\text{H}_{45}\text{N}_3\text{O}_6 \cdot 0.47$ $\text{H}_2\text{O}$		
	Calc.	Found
C	66.00	65.89
H	8.21	8.00
N	7.45	7.56

#### Example 161

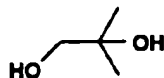
Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,1-dimethylethyl ester (Compound 161g)

##### (a) Compound 161a

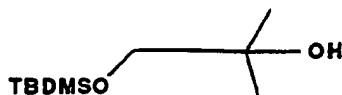


A mixture of Compound 44a (1.0 g, 3.36 mmol) and 5% Pd on  $\text{CaCO}_3$ , poisoned with Pb (0.1 g, Aldrich) in 40 mL of MeOH was stirred under 1 atm  $\text{H}_2$  for 2 h. The catalyst was filtered off through a pad of Celite and the filtrate concentrated. The crude product was purified by chromatography on a column of silica gel (2.5 X 35cm) eluting with a gradient of  $\text{CH}_2\text{Cl}_2$ -MeOH-aqueous  $\text{NH}_4\text{OH}$  (98.0-1.8-0.2 to 95.0-4.5-0.5) to afford 170 mg (31% yield) of Compound 161a as a clear oil.

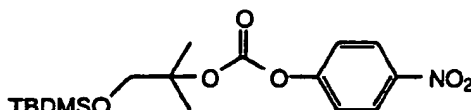
##### (b) Compound 161b



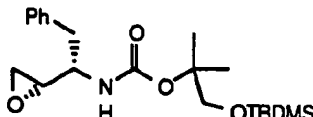
To 26.25 mL of 0.1 M  $\text{HClO}_4$  was slowly added 9.45 g (0.131 mol) of isobutylene oxide and the reaction mixture stirred at RT for 30 mins. Water from the reaction mixture was distilled off first, followed by the product which distilled at 80°C (10 mm Hg). Collection of pure distillate afforded Compound 161b as a colorless oil (6.4 g, 54%).

(c) Compound 161c

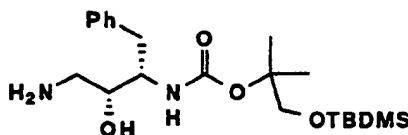
10 To a cooled (0°C) solution of Compound 161b (2.0 g, 22.22 mmol) in 10 mL of CH<sub>2</sub>Cl<sub>2</sub> was added Et<sub>3</sub>N (6.2 mL, 44.44 mmol) followed by *t*-butyldimethylsilyl chloride (3.684 g, 24.44 mmol). The reaction mixture was warmed to RT and after 2 h of stirring, N,N-dimethylaminopyridine (0.056 g, 0.44 mmol) was added. After stirring the reaction mixture overnight, it was diluted with EtOAc and washed with saturated NaHCO<sub>3</sub> followed by brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated. The crude product obtained was chromatographed on silica gel eluting with a stepwise gradient of hexane to 50% EtOAc-hexane to afford Compound 161c (4.2 g, 92%) as a colorless oil.

(d) Compound 161d

25 To a solution of Compound 161c (1.0 g, 4.9 mmol) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 5.0 mL of pyridine followed by slow addition of a solution of *p*-nitrophenylchloroformate (1.185 g, 5.88 mmol) in 6 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resulting suspension was stirred at 5°C overnight. The reaction mixture was diluted with EtOAc and washed with saturated NaHCO<sub>3</sub> and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to obtain the crude product which was flash chromatographed on silica gel eluting with a stepwise gradient of hexane to 10% EtOAc-hexane to afford Compound 161d (1.05 g, 58%) as a viscous oil.

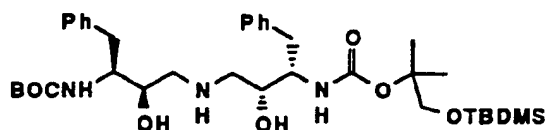
(e) Compound 161e

40 A solution of Compound 161a (70 mg, 0.429 mmol), Compound 161d (174 mg, 0.472 mmol), and *i*-Pr<sub>2</sub>NEt (90 µL, 66.5 mg, 0.515 mmol) in 0.5 mL DMF was stirred at RT for 72 h. The crude mixture was combined with the crude mixture of a second, similar reaction run on exactly twice the scale. The combined crude mixture was concentrated and chromatographed on a column of silica gel (2.5X30cm) eluting with 10% EtOAc-hexane to afford 423 mg (83% yield) of Compound 161e as a clear oil.

(f) Compound 161f

55 A stream of NH<sub>3</sub> was bubbled into a 5°C solution of Compound 161e (420 mg, 1.07 mmol) in 5 mL EtOH and 5 mL 30% aqueous NH<sub>4</sub>OH for 30 min. The resulting solution was stirred at 5°C for 15 min and then at RT for 18 h. Argon was bubbled through the mixture for a few minutes and the solvents were removed. The crude product was chromatographed on a column of silica gel (2.5X15cm) eluting with a gradient of CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aqueous NH<sub>4</sub>OH (98.0-1.8-0.2 to 92.0-7.2-0.8) to afford 373 mg (85% yield) of Compound 161f as a white solid.

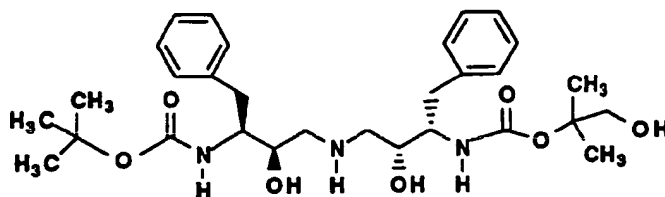


(g) Comp und 161g

A solution of Compound 161f (223 mg, 0.543 mmol) and Compound 1b(i) (129 mg, 0.489 mmol) was stirred in 1 mL of DMF at 115°C for 3.5 h. The mixture was cooled to RT, concentrated to remove the bulk of the DMF, and the crude product was chromatographed on a column of silica gel (2.5X25cm) eluting with a gradient of CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aqueous NH<sub>4</sub>OH (98.0-1.8-0.2 to 92.0-7.2-0.8) to afford 176 mg (53% yield) of Compound 161g as a white solid.

Example 162

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl-2-hydroxy-1,1-dimethylethyl ester (Compound 162)

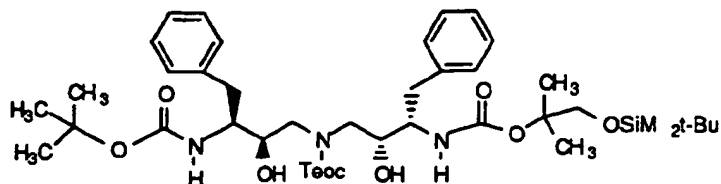


To a solution of Compound 161g (170 mg, 0.252 mmol) in 1 mL THF was added 3 mL HOAc followed by 1 mL of H<sub>2</sub>O. The resulting mixture was stirred at RT for 32 h. Solvents were removed and the crude product was chromatographed on a column of silica gel (2.5X25cm) eluting with a gradient of CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aqueous NH<sub>4</sub>OH (98.0-1.8-0.2 to 92.0-7.2-0.8) to afford 107 mg (76% yield) of the title Compound 162 as a white solid. (Alternatively, Compound 157b was converted to Compound 162 by a procedure analogous to that used for the synthesis of Compound 2.)  
m.p. 153 - 155°C; [α]<sub>D</sub> = -6.5° (c 0.54)

Elemental Analysis (%) for C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>7</sub>		
	Calc.	Found
C	64.38	64.07
H	8.10	8.16
N	7.51	7.91

Example 163

Preparation of [R-(R\*,S\*)]-[[(Trimethylsilyl)ethoxy]carbonyl]iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 2-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,1-dimethylethyl ester (Compound 163)



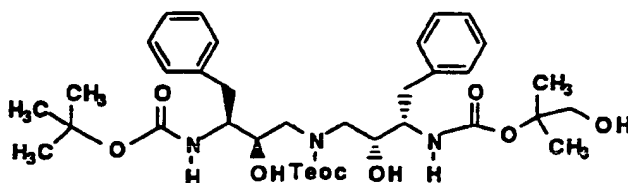
Compounds 161d and 48 were reacted by a procedure analogous to that used for the synthesis of Compound 143 ( $i\text{-Pr}_2\text{NEt}$  used as base) to give the title Compound 163 (white solid).

$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.23 - 7.08 (m, 10H) 4.13 (m, 2H) 3.81 - 3.60 (m, 6H) 3.5 - 3.36 (m, 2H) 3.30 (m, 2H) 3.03 (m, 2H) 2.59 (m, 2H) 1.30 - 1.08 (15H) 0.98 (m, 2H).

Mass Spec (FAB) -  $(\text{M} + \text{H})^+ = 704$

#### Example 164

Preparation of [R-(R\*,S\*)]-III[(Trimethylsilyl)-ethoxy]carbonyl]iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 2-hydroxy-1,1-dimethylethyl ester (Compound 164)



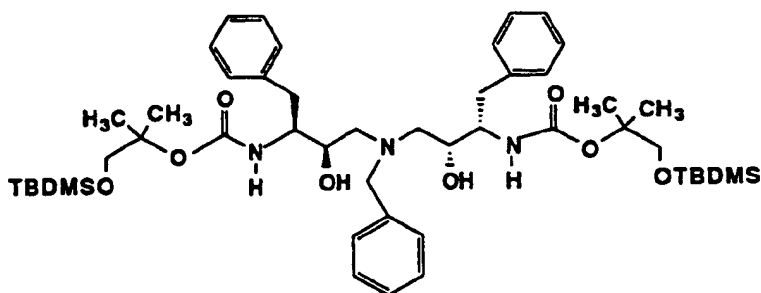
Compound 163 was converted to the title Compound 164 (white foam) by a procedure analogous to that used for Compound 162.

TLC ( $\text{SiO}_2$ )  $R_f = 0.22$  (50% EtOAc/Hexanes - PMA). Compound 164 was converted to Compound 162 in 20% yield by a procedure analogous to that used for Compound 21.

#### Example 165

Preparation of [R-(R\*,S\*)]-I[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, bis(2-hydroxy-1,1-dimethylethyl) ester (Compound 165c)

##### (a) Compound 165a

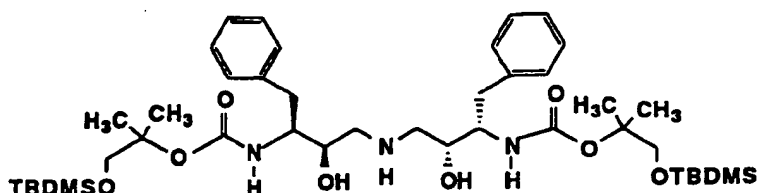


Compounds 32 and 161d (2 eq.) were reacted by a procedure analogous to that used for the synthesis of Compound 161e to give Compound 165a.

(b) Compound 165b

5

10



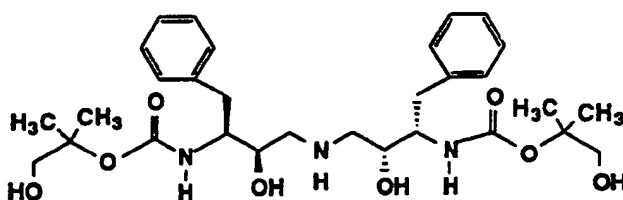
Compound 165a was converted into Compound 165b (white solid) by a procedure analogous to that used for the synthesis of Compound 2.

15

(c) Compound 165c

20

25



Compound 165b was converted to Compound 165c by a procedure analogous to that used for the synthesis of Compound 162.

mp 140-142 °C;  $[\alpha]_D^{20} = -2.3^\circ$  (c = 0.2, CH<sub>3</sub>OH).

30 Mass Spec. (FAB) (M + H)<sup>+</sup> = 576;

Analysis calc. for C<sub>30</sub>H<sub>45</sub>N<sub>3</sub>O<sub>8</sub>·1.42H<sub>2</sub>O:

Calculated C, 59.93; H, 8.02; N, 6.99;

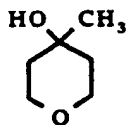
Found: C, 60.14; H, 7.68; N, 6.78.

35 Example 166

Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl-4-methyltetrahydropyran-4-yl-ester (Compound 166b)

40 (a) Compound 166a

45

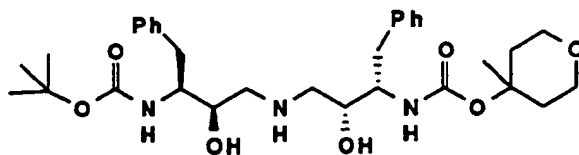


Tetrahydro-4H-pyran-4-one was converted to Compound 166a by a procedure analogous to that used for the synthesis of Compound 149c.

50

(b) Compound 166b

55



Compound 166a was converted to the title Compound 166b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

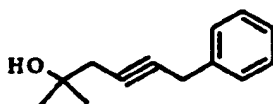
m.p. 144 - 146°C

Elemental Analysis (%) C <sub>32</sub> H <sub>47</sub> N <sub>3</sub> O <sub>7</sub> · 0.54 H <sub>2</sub> O		
	Calc.	Found
C	64.55	64.64
H	8.14	8.02
N	7.06	6.97

### Example 167

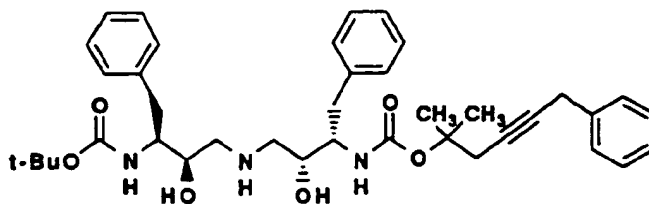
Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 1,1-dimethyl-5-phenyl-3-pentynyl ester (Compound 167b)

#### (a) Compound 167a



To a -78°C solution of 3-phenyl-1-propyne (4.00 g; 34.4 mmol) in THF (16 mL) was added a solution of n-BuLi (14.10 mL of a 2.52 M solution in hexanes) followed 30 min later by BF<sub>3</sub>·Et<sub>2</sub>O (4.24 mL; 34.5 mmol). The resulting solution was stirred at -78°C for 1 h at which point a solution of isobutylene oxide (2.55 g; 35.4 mmol) in THF (5 mL) was added. After 2 hr, a saturated aqueous NaHCO<sub>3</sub> solution was added and the mixture was allowed to warm to RT. The mixture was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O and the combined organic extracts washed with H<sub>2</sub>O and brine, dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an orange-yellow oil. This material was chromatographed on silica gel (200 mL) using 10:1 hexane:EtOAc as eluent to give Compound 167a (4.32 g; 67%) as a pale yellow oil.

#### (b) Compound 167b



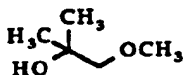
Compound 167a was converted to the title Compound 167b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

m. p. 120-124°C; [α]<sub>D</sub> = -3.2° (c 0.25, MeOH)

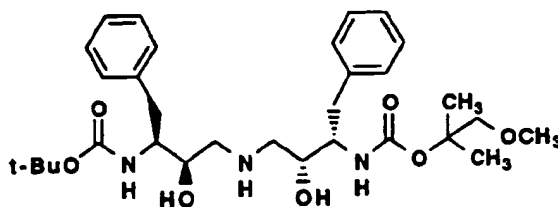
Mass sp c (CI) 658 (M+H)

**Example 168**

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl 2-methoxy-1,1-dimethylethyl ester (Compound 168b)

**(a) Compound 168a**

Methylmethoxy acetate was converted to Compound 168a by a procedure analogous to that used for the synthesis of Compound 149c.

**(b) Compound 168b**

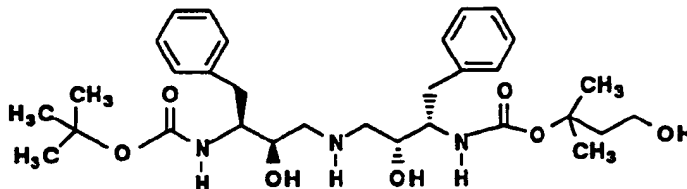
Compound 168a was converted to the title Compound 168b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate to Compound 48).

m.p. 151-155°C;  $[\alpha]_D = -5.8^\circ$  (c 0.32, MeOH)

Mass spec (CI) 574 (M+H)

**Example 169**

Preparation of [1S-(1R\*,2S\*)]-Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-3-hydroxy-1,1-dimethylpropyl ester (Compound 169)



Compound 169 was obtained as a white solid from Compound 158b by a procedure analogous to that used for the synthesis of Compound 2.

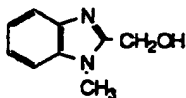
m.p. 133°C;  $[\alpha]_D^{20} = -5.0^\circ$  (c 0.2, CH<sub>3</sub>OH)

Elemental Analysis (%) Calculated for $C_{31}H_{47}N_3O_7 \cdot 0.95 H_2O$		
	Calc.	Found
C	63.02	62.98
H	8.34	8.18
N	7.11	7.15

### Example 170

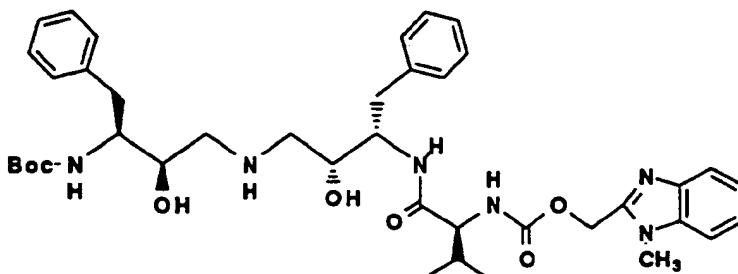
Preparation of S-[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[[[(1-methyl-1H-benzimidazol-2-yl)methoxy]carbonyl]-L-valinamide (Compound 170b)

#### (a) Compound 170a



A mixture of 2-hydroxymethylbenzimidazole (500 mg, 3.38 mmol), anhydrous  $K_2CO_3$  (467 mg, 3.38 mmol) and MeI (210  $\mu$ l, 3.38 mmol) in 5 ml of DMF was heated at 50°C for 6 hr. The reaction was diluted with  $H_2O$  and extracted with EtOAc. The extracts were washed with brine, dried ( $Na_2SO_4$ ) and concentrated. The crude product was purified on a 30 ml silica column eluting with MeOH:EtOAc (1:9) to give 146 mg (27%) of Compound 170a.

#### (b) Compound 170b



Compound 170a was converted into the title Compound 170b by a three-step sequence analogous to that used for the synthesis of Compound 67c (pyridine was used in the formation of the p-nitrophenyl carbonate; no t-BuOH was used in the coupling of the p-nitrophenyl carbonate with L-valine; and no  $CH_2Cl_2$  was used in the reaction of the resulting acid with Compound 54).

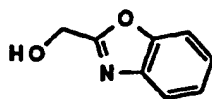
m.p. 148-152°C;  $[\alpha]_D = -18.6^\circ$  (c = 0.22, MeOH)

High Res. Mass Spec. (FAB):  $C_{40}H_{55}N_6O_7 = 731.4142^+$ ;  $\Delta = 1.4$  ppm.

### Example 171

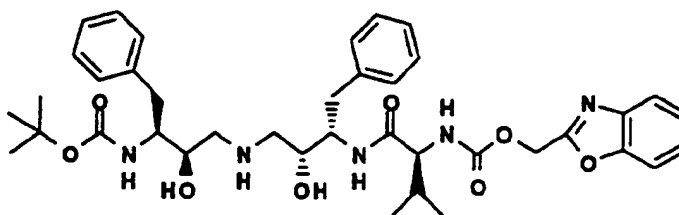
Preparation of S-[1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[[[(2-Benzoxazolyl)methoxy]carbonyl]-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 171b)

**(a) Compound 171a**



To a mixture of 2.50 g (22.9 mmol) of *o*-aminophenol and 1.74 g (22.9 mmol) of glycolic acid in 50 mL of toluene was added 150 mg of *p*-toluenesulfonic acid. The mixture was heated at reflux for 18 h with azeotropic removal of water. The resulting solution was cooled to RT, diluted with EtOAc and washed with 1N NaOH. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through a pad of silica gel, and concentrated *in vacuo* to give 1.57 g (47%) of an orange solid which was recrystallized from EtOAc-hexane to afford 647 mg of Compound 171a (yellow solid).

**(b) Compound 171b**



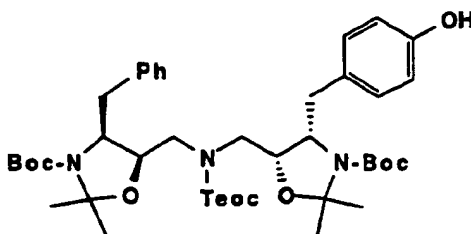
Compound 171a was converted into the title Compound 171b by a three-step sequence analogous to that used for the synthesis of Compound 67c (pyridine was used in the formation of the p-nitrophenyl carbonate; no t-BuOH was used in the coupling of the p-nitrophenyl carbonate with L-valine; and no CH<sub>2</sub>Cl<sub>2</sub> was used in the reaction of the resulting acid with Compound 54).  
m.p. 186-188°C

Elemental Analysis Calc. for $C_{39}H_{51}N_5O_8 \cdot 0.82 H_2O$			
	C, 63.93;	H, 7.24;	N, 9.56
Found	C, 64.02	H, 7.13	N, 9.47

**Mass spec (FAB) 718 (M+H)**

### Example 172

**Preparation of [4S-4 $\alpha$ ,5 $\alpha$ (4R\*,5S\*)]-5-[-3-[(1,1-Dimethylethoxy)carbonyl]-4-[(4-hydroxyphenyl)methyl]-2,2-dimethyl-5-oxazolidinyl)methyl][2-(trimethylsilyl)ethoxy]carbonyl]amino)methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinonecarboxylic acid, 1,1-dimethylethyl ester (Compound 172)**



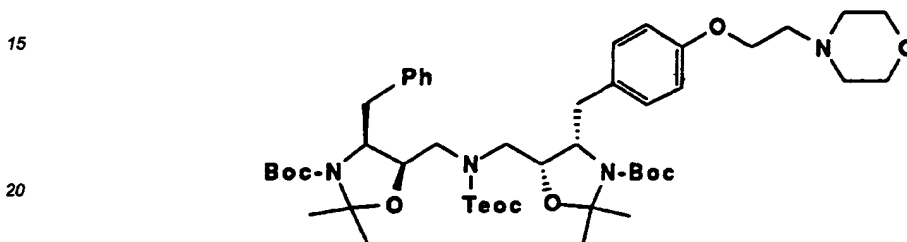
The mixture of Compound 20 (211 mg, 0.30 mmol), 2,2-dimethoxypropane (250 mg, 2.4 mmol) and *p*-TsOH (1.5 mg) in dry benzene (1.6 ml) was refluxed for 3.0 hrs with azeotropic removal of H<sub>2</sub>O, then stirred at RT

overnight. The mixture was diluted with EtOAc then washed with saturated NaHCO<sub>3</sub> and brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (hexane/EtOAc 10:1 to 6:1) on a silica gel column (190 x 20 mm) afforded 230 mg (98%) of Compound 172 as a white foam.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 6.65-7.40 (m, 11H), 4.04-4.38 (m, 6H), 3.20-3.64 (m, 4H), 2.81-3.06 (m, 4H), 1.25-1.94 (m, 30H), 0.95 (m, 2H), 0.00 (s, 9H).

#### Example 173

Preparation of [4S-4α,5α(4R\*,5S\*)]-5-[[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2-dimethyl-4-[[4-[2-(4-morpholinyl)ethoxy]phenyl]methyl]-5-oxazolidinyl]methyl][2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester (Compound 173)

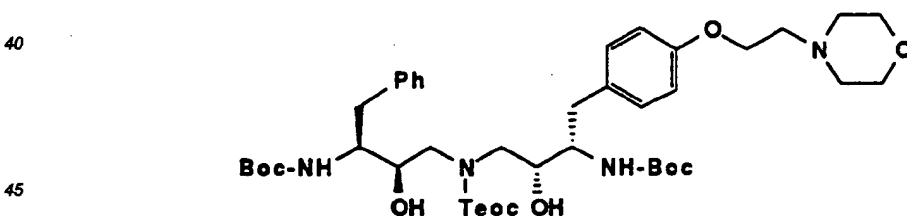


The mixture of Compound 172 (200 mg, 0.255 mmol), 4-(2-chloroethyl)morpholine (191 mg, 1.28 mmol) and K<sub>2</sub>CO<sub>3</sub> (88 mg, 0.638 mmol) in dry DMF (1.0 ml) was heated at 100°C for 14 hrs. The mixture was diluted with EtOAc then washed with water, saturated NaHCO<sub>3</sub> and brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (100% CHCl<sub>3</sub> to CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH: 99:1:0.1) on a silica gel column (200 x 20 mm) afforded 163 mg (71%) of Compound 173 as a colorless oil.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 7.10-7.40 (m, 7H), 6.84 (m, 2H), 4.02-4.39 (m, 8H), 3.76 (t, J = 4.70, 4H), 3.20-3.60 (m, 4H), 2.73-3.03 (m, 6H), 2.60 (m, 4H), 1.24-1.83 (m, 30H), 0.95 (m, 2H), 0.00 (s, 9H).

#### Example 174

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)ethoxy]phenyl]butyl][2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamic acid, 1,1-dimethylethyl ester (Compound 174)



To Compound 173 (160 mg, 0.178 mmol) was added pre-cooled (10°C) 96% formic acid (8.0 ml). The mixture was stirred at 5°C for 15 min then was frozen (dry ice-acetone) and lyophilized overnight. The residue was taken into CHCl<sub>3</sub> and washed with saturated NaHCO<sub>3</sub> and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (100% CHCl<sub>3</sub> to CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH: 98:2:0.2) on a silica gel column afforded 112 mg (77%) of Compound 174 as a colorless oil.

<sup>1</sup>H-NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): 7.10-7.30 (m, 7H), 6.78 (m, 2H), 4.45-4.85 (m, 3H), 4.13 (t, J = 8.76, 2H), 4.00 (t, J = 5.77, 2H), 3.55-3.90 (m, 4H), 3.63 (t, J = 4.70, 4H), 3.10-3.55 (m, 4H), 2.60-2.95 (m, 4H), 2.70 (t, J = 5.77, 2H), 2.48 (m, 4H), 1.31 and 1.30 (both s, 18H), 0.96 (m, 2H), 0.00 (s, 9H).

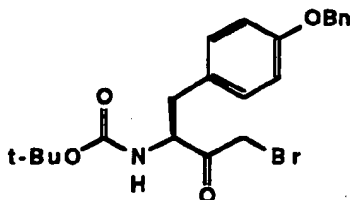
#### Example 175

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-[2-(4-



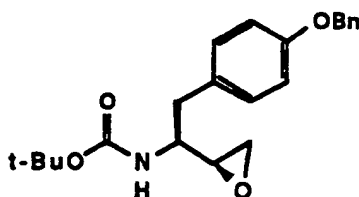
morpholinyl)ethoxy]phenyl]butyl]aminyl]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 175 )

(a) Compound 175a

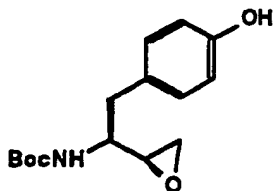


To a solution of N-Boc-o-benzyl-L-tyrosine (25 g, 67.3 mmol) in dry THF (90 ml) cooled at -20°C to -25°C was added isobutyl chloroformate (8.7 ml, 67.3 mmol) followed by 4-methylmorpholine (6.8 ml, 67.3 mmol) and the mixture was stirred for 20 min. The precipitate was filtered and washed with dry THF. The filtrate was cooled to -5°C and poured into a diazomethane in ether solution (prepared from 1-methyl-3-nitro-1-nitroso-guanidine (29.7 g, 202 mmol) as described in Example 1a(i)) at 0°C. The resulting yellow solution was kept at 0°C for 2.0 h, then at RT overnight. Nitrogen was then bubbled through the solution for 30 min, the solution diluted with Et<sub>2</sub>O (500 ml) and then washed with H<sub>2</sub>O, sat'd NaHCO<sub>3</sub>, and brine, and dried (MgSO<sub>4</sub>). Concentration *in vacuo* afforded a yellow residue, which was triturated with hexane (500 ml) to give 24.5 g (92%) of the corresponding α-diazoketone as an off-white solid. A solution of 48% aqueous HBr (5.8 ml, 51.4 mmol) was added dropwise to the α-diazoketone (20.3 g, 51.4 mmol) in 500 ml of 1,4-dioxane-DME (2:1) cooled at -5°C. After 30 min, saturated NaHCO<sub>3</sub> was added until pH = 7.0 and the solvent was removed under reduced pressure. The mixture was diluted with H<sub>2</sub>O and extracted with EtOAc. The combined organic extracts were washed with H<sub>2</sub>O and brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration *in vacuo* followed by recrystallization from EtOAc-hexane gave 20.9 g (91%) Compound 175a as an off-white solid.

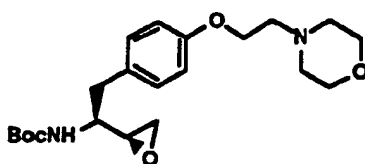
(b) Compound 175b



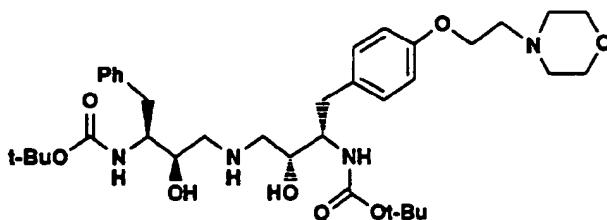
To a solution of Compound 175a (23.3 g, 50.0 mmol) in 250 ml of MeOH-THF (1:1) cooled at -5°C was added, portionwise, NaBH<sub>4</sub> (2.0 g, 50.0 mmol). After 1 h, 10% KHSO<sub>4</sub> (75 ml) was added at 0°C and the mixture was allowed to warm to RT. The mixture was extracted with hot EtOAc and the combined organic extracts were washed with H<sub>2</sub>O and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration *in vacuo* followed by recrystallization from EtOAc (350 ml) afforded 14.5 g (62%) of the *syn* bromohydrin as a white solid. HPLC analysis showed the diastereomeric ratio as 95:5. To a solution of the *syn* bromohydrin, prepared as above (115.2 g, 0.256 mole), in 1.5 L of THF and 1.5 L of 100% EtOH was added a solution of KOH (17.2 g of 87.6% pellets, 0.269 mole) in 300 mL of 100% EtOH at RT. After 15 min, 1 L of sat. aq. NH<sub>4</sub>Cl was added and the mixture then diluted with 6 L of H<sub>2</sub>O to give a precipitate. The solid was filtered, washed with H<sub>2</sub>O, and extracted into 1 L of EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a solid which was triturated with 1 L of hexane, to afford 79.3 g (84%) of Compound 175b as a white solid.

(c) Compound 175c

The mixture of Compound 175b (5.0 g, 13.5 mmol) and  $\text{Pd}(\text{OH})_2$  (500 mg) in 100 ml EtOH and 25 ml of EtOAc was stirred under hydrogen atmosphere for 4.5 hrs. The catalyst was removed by filtration and the filter cake was washed with EtOH, MeOH, and EtOAc. The combined washes were concentrated *in vacuo* to give a 3.8 g (99%) of Compound 175c as a white solid.

(d) Compound 175d

To the mixture of Compound 175c (150 mg, 0.54 mmol), 4-(2-hydroxyethyl)morpholine (141 mg, 1.07 mmol) and  $\text{PPh}_3$  (282 mg, 1.07 mmol) in 1.5 ml of dry THF was added DEAD (169  $\mu\text{l}$ , 1.07 mmol). The resulting mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography ( $\text{CHCl}_3$ -i-PrOH- $\text{NH}_4\text{OH}$ : 99:1:0.1 to 98:2:0.2) afforded 190 mg (90%) of Compound 175d as a white foam.

(e) Compound 175e

A mixture of Compound 175d (126 mg, 0.32 mmol) and Compound 16b (90 mg, 0.32 mmol) in 0.64 ml of dry DMF was heated at 100°C for 4.0 hrs. Concentration *in vacuo* followed by flash chromatography ( $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 99:1:0.1 to 96:4:0.4) afforded, after trituration with chloroform/hexane, 90 mg (44%) of Compound 175e.

m.p.: 140.0-141.0°C;  $[\alpha]_D = -3.25^\circ$  (c 0.246, MeOH).

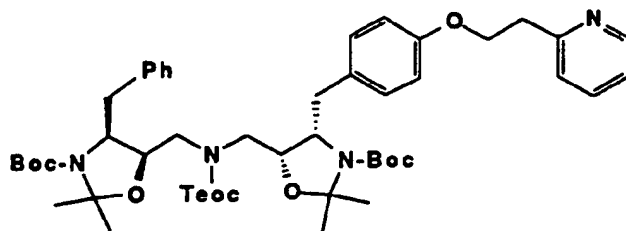
MS (FAB): 673<sup>+</sup> ( $\text{M}+\text{H}$ )<sup>+</sup>.

Anal. Calc. for  $\text{C}_{38}\text{H}_{56}\text{N}_4\text{O}_8 \cdot 0.42\text{H}_2\text{O}$ : C, 63.55; H, 8.42; N, 8.24. Found: C, 63.73; H, 8.43; N, 8.06.

Alternatively, Compound 175e was prepared as follows. Compound 174 was converted to the title Compound 175e by a procedure analogous to that used for the synthesis of Compound 21. Flash chromatography (100%  $\text{CHCl}_3$  to  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 100:4.5:0.5) on a silica gel column gave Compound 175e as a white solid which was lyophilized from 1,4-dioxane to give a white lyophilate.

Example 176

Preparation of [4S-4 $\alpha$ ,5 $\alpha$ (4R\*,5S\*)]-5-[[[3-[(1,1-Dimethylethoxy)carbonyl]-2,2-dimethyl-4-phenylmethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester (Compound 176)

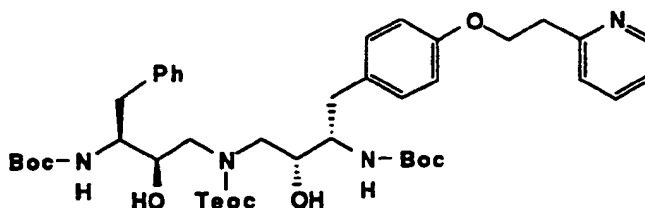


To the mixture of Compound 172 (184 mg, 0.235 mmol), 2-(2-hydroxyethyl)pyridine (40  $\mu$ l, 0.352 mmol) and  $\text{PPh}_3$  (93 mg, 0.352 mmol) in dry THF (0.5 ml) was added DEAD (55  $\mu$ l, 0.352 mmol). The resulting yellow solution was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (hexane/EtOAc 4:1) on a silica gel column afforded 143 mg (69%) of Compound 176 as a colorless oil.

$^1\text{H-NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ): 8.49 (d,  $J = 5.13$ , 1H), 7.79 (m, 1H), 7.44 (d,  $J = 7.69$ , 1H), 7.13-7.38 (m, 8H), 6.87 (d,  $J = 7.69$ , 1H), 4.34 (t,  $J = 6.41$ , 2H), 4.03-4.35 (m, 6H), 3.30-3.55 (m, 4H), 3.26 (t,  $J = 6.41$ , 2H), 2.75-3.00 (m, 4H), 1.30-1.79 (m, 30H), 0.93 (m, 2H), 0.00 (s, 9H).

#### Example 177

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-[[4-2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 177)



#### a) Removal of bis-acetonide

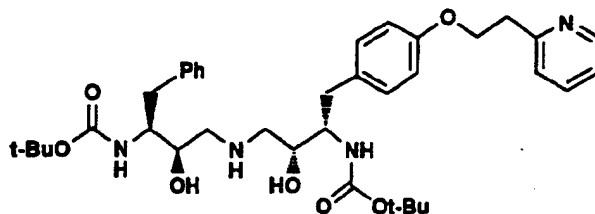
To Compound 176 (143 mg, 0.161 mmol) was added pre-cooled ( $10^\circ\text{C}$ ) 96% formic acid (4.0 ml). The mixture was stirred at  $5^\circ\text{C}$  for 15 min then was frozen (dry ice-acetone) and lyophilized overnight to give an oily residue.

b) The above residue was dissolved in MeOH (2.3 ml). To this solution was added  $\text{Et}_3\text{N}$  (40  $\mu$ l, 0.242 mmol) and di-*t*-butyldicarbonate (20  $\mu$ l, 0.08 mmol). The mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (100%  $\text{CHCl}_3$  to  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 97:3:0.3) on a silica gel column afforded 106 mg (81%) of Compound 177 as a white foam.

$^1\text{H-NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ): 8.42 (m, 1H), 7.72 (m, 1H), 7.36 (m, 1H), 7.03-7.25 (m, 8H), 6.75 (d,  $J = 7.69$ , 2H), 4.24 (t,  $J = 6.41$ , 2H), 4.12 (t,  $J = 8.55$ , 2H), 3.50-3.80 (m, 6H), 3.17 (t,  $J = 6.41$ , 2H), 2.88-3.30 (m, 4H), 2.35-2.64 (m, 2H), 1.25 (s, 18H), 0.99 (t,  $J = 8.55$ , 2H), 0.00 (s, 9H).

#### Example 178

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 178)



A mixture of Compound 177 (0.106 g; 0.131 mmol) and solid  $n\text{-Bu}_4\text{NF}\cdot n\text{H}_2\text{O}$  (0.103 g; 0.393 mmol) in 0.56 ml THF was stirred at  $50^\circ\text{C}$  for 4 h. After cooling to RT, 1 g of celite was added and the solvent removed *in vacuo*. Flash chromatography ( $\text{CHCl}_3\text{-MeOH-NH}_4\text{OH}$ : 98:2:0.2 to 95:5:0.5) on a silica gel column followed by trituration with  $\text{Et}_2\text{O-hexane}$  gave 0.04 g of Compound 178 as a light yellow solid.

m.p.:  $125.0\text{-}126.5^\circ\text{C}$ ;  $[\alpha]_D = -4.84^\circ$  (c 0.248, MeOH).

MS (FAB):  $665^+$  ( $\text{M}+\text{H}$ ) $^+$ .

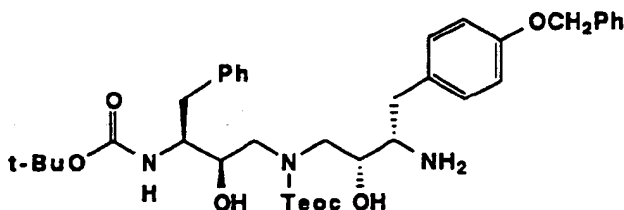
Anal. Calc. for  $\text{C}_{37}\text{H}_{52}\text{N}_4\text{O}_7\cdot 0.53\text{H}_2\text{O}$ :

	C, 65.89;	H, 7.93;	N, 8.13.
Found:	C, 66.07;	H, 7.85;	N, 8.13.

#### Example 179

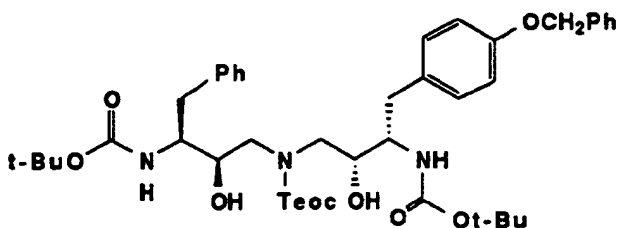
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-(phenylmethoxy)phenyl]methyl]propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 179c)

##### (a) Compound 179a

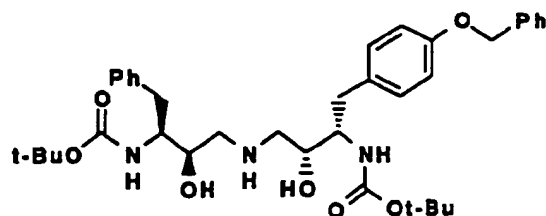


Compound 18 was converted to Compound 179a in 27% yield by a procedure analogous to that used for the synthesis of Compound 19 except that the reaction was only allowed to proceed to partial completion.

##### (b) Compound 179b



Compound 179a was converted to Compound 179b by a procedure analogous to that used for the synthesis of Compound 131 except that MeOH was used in place of DMF and the reaction was run at RT overnight.

(c) Compound 179c

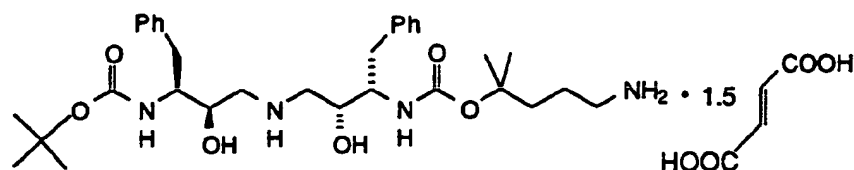
Compound 179c was obtained as a white solid from Compound 179b by a procedure analogous to that used for the synthesis of Compound 21.

m.p. 159 - 161°C;  $[\alpha]_D = -8.97^\circ$  (c 0.245, DMSO)

M.S. (FAB): 650<sup>+</sup> (M + H)<sup>+</sup>

Example 180

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 4-amino-1,1-dimethylethyl 1,1-dimethylethyl ester, fumarate (2:3) salt (Compound 180)]



Compound 180 was obtained as a white powder from Compound 150 by a procedure analogous to that used for the synthesis of Compound 84.

mp 123-130°C;  $[\alpha]_{365} = -12.7$  (c 0.15, MeOH).

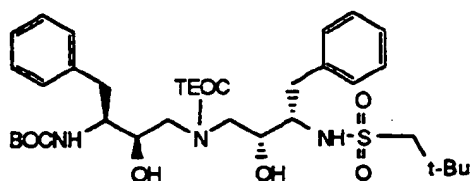
Mass Spec. FAB + ions: (M+H)= 587.

Analysis calc. for C<sub>32</sub>H<sub>50</sub>N<sub>4</sub>O<sub>6</sub> · 1.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> · 2.96 H<sub>2</sub>O:

	C, 56.06;	H, 7.66;	N, 6.88;
Found:	C, 56.21;	H, 7.42;	N, 6.73.

Example 181

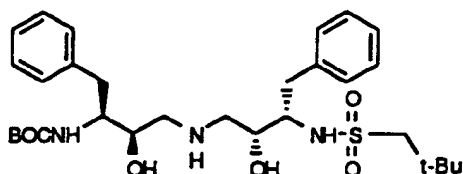
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,2-Dimethylpropyl)sulfonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 181b)]

(a) Compound 181a

To a stirred solution of Compound 48 (300 mg, 0.51 mmol) in 2 ml of dry CH<sub>3</sub>CN at -20°C under argon was

added 2,2-dimethylpropyl-1-sulfonylchloride (*Synthesis*, 489 (1974)) (96 mg, 0.56 mmol) followed by *i*-Pr<sub>2</sub>NEt (79 mg, 0.61 mmol). After approximately 2 hr at -5°C, additional sulfonylchloride (48 mg, 0.28 mmol) and *i*-Pr<sub>2</sub>NEt (40 mg, 0.31 mmol) was added at -20°C. The mixture was re-warmed to ca. -5°C and stirred at that temperature for 4 hr, at which time the solution was adsorbed onto celite and chromatographed on a column (2.5X30cm) of silica gel eluting with a gradient of hexane and EtOAc to afford 101 mg (27% yield) of Compound 181a as a clear solid foam.

(b) Compound 181b



Compound 181b was obtained as a white lyophilate from Compound 181a by a procedure analogous to that used for the synthesis of Compound 21.

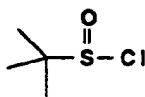
m.p. 134 - 137°C ("shrinkage" at 65 - 134°C);  $[\alpha]_D = -11.0^\circ$  (c 0.77, MeOH)

Elemental Analysis (%) Calc. for $C_{30}H_{47}N_3O_6S \cdot 0.7 H_2O$		
	Calc.	Found
C	61.03	61.05
H	8.26	8.17
N	7.12	7.10

Example 182

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[(1,1-Dimethylethyl)-sulfinyl]amino-2-hydroxy-4-phenylbutyl]amino-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 182c)

(a) Compound 182a

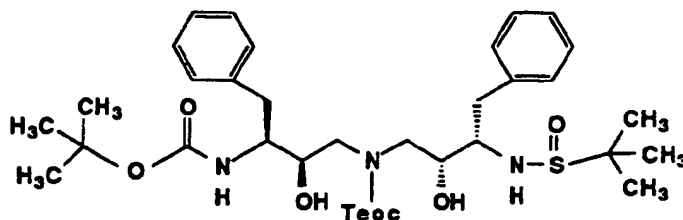


To a solution of *t*-butyl disulfide (4.8 mL, 25 mmol) in 25 mL of HOAc at 0°C was added 3.18 mL (31.25 mmol) of 30% aqueous H<sub>2</sub>O<sub>2</sub>. The reaction mixture was stirred at 5°C for 24 h and then poured into 100 mL of ice water. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined extracts washed with sat. NaHSO<sub>3</sub>, sat. NaHCO<sub>3</sub> and H<sub>2</sub>O. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to obtain a colorless oil. Cl<sub>2</sub> gas (1.93 g, 27.18 mmol) was condensed at -78°C and cannulated into a cooled solution (0-10°C) of the above oil in 25 mL of dry CH<sub>2</sub>Cl<sub>2</sub>. The resulting yellow solution was allowed to warm to RT and concentrated to obtain a dark yellow oil which was distilled at 47-48°C (9 mm Hg) to obtain pure Compound 182a (0.72 g, 20%) as a colorless oil.

(b) Compound 182b

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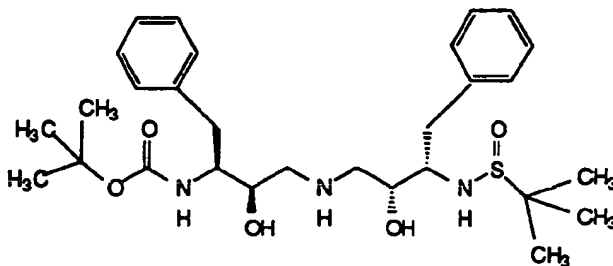
15

Compound 182a was converted to Compound 182b by a procedure analogous to that used for the synthesis of Compound 181a except that  $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$  was used.

(c) Compound 182c

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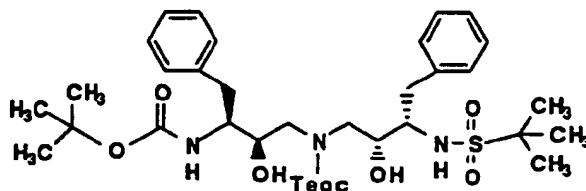
Compound 182c was prepared as a white solid from Compound 182b by a procedure analogous to that used for Compound 21.  
m.p. 152-155°C ("shrinkage" at 55-70°C)

35 Example 183

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,2-dimethylethyl)sulfonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 183b)

40 (a) Compound 183a

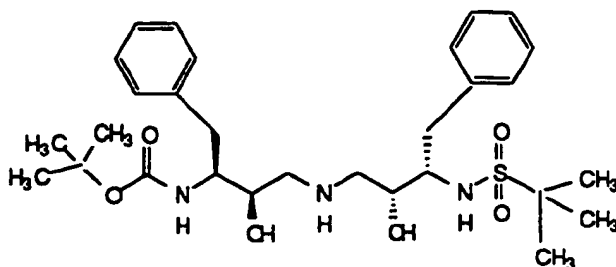
45



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To a solution of Compound 182b (0.22 g, 0.318 mmol) in 2.5 mL of  $\text{CH}_2\text{Cl}_2$  cooled to 0°C was added 1.5 mL of saturated aq.  $\text{NaHCO}_3$ . The suspension was vigorously stirred and a solution of 75% *m*-CPBA (80 mg, 0.35 mmol) in 2.5 mL of  $\text{CH}_2\text{Cl}_2$  was added dropwise. The reaction mixture was stirred for 90 min after which time it was warmed to RT, diluted with  $\text{CH}_2\text{Cl}_2$  and washed with sat.  $\text{NaHSO}_3$  followed by sat.  $\text{NaHCO}_3$ . The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated. The crude material was flash chromatographed on silica eluting with a step-wise gradient of 25% EtOAc-hexane to 80% EtOAc-hexane to obtain 0.193 g (85%) of Compound 183a as a white solid.

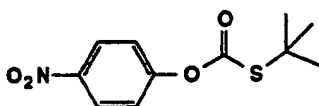
(b) Compound 183b

Compound 183b was prepared as a white solid by a procedure analogous to that used for the synthesis of Compound 21.

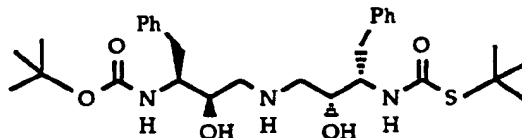
m.p. 86-90°C ("softening" at 75-86°C);  $[\alpha]^{20}_D = -18.7^\circ$  ( $c = 0.2$ , CH<sub>3</sub>OH).

Example 184

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethyl)thio]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 184b)

(a) Compound 184a

Compound 184a was prepared from t-butyl mercaptan by a procedure analogous to that used for the synthesis of Compound 67a (pyridine was used).

(b) Compound 184b

Compounds 184a and 54 were reacted by a procedure analogous to that used for the synthesis of Compound 147d to afford Compound 184b as a white solid.

m.p. 140-141°C ("softening" at 134 - 140°C);  $[\alpha]^{20}_D = -20.0^\circ$  ( $c = 0.05$ , CH<sub>3</sub>OH).

Example 185

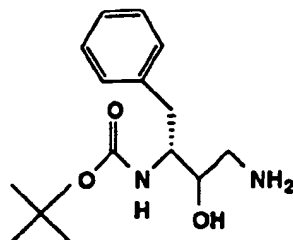
Preparation of [2S-[2R\*,3S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, phenylmethyl ester (Compound 185d)



(a) Compound 185a

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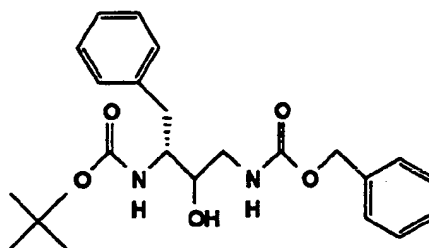
15

A 3:2 mixture of Compounds 26a(i) and 26a(ii) was converted into Compound 185a by a procedure analogous to that used for the synthesis of Compound 16b (except that the reaction was performed in  $\text{NH}_3$  saturated MeOH at 50-60°C in a sealed vessel).

(b) Compound 185b

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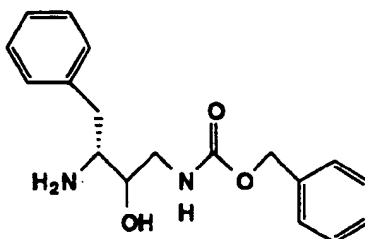
Compound 185a was reacted with Cbz chloride by a procedure analogous to that used for the synthesis of Compound 122 to give Compound 185b ( $\text{CH}_2\text{Cl}_2$  used in place of DMF).

(c) Compound 185c

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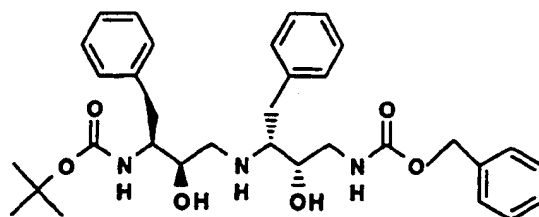
45



Compound 185b was converted to Compound 185c by a procedure analogous to that used for the synthesis of Compound 32.

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(d) Compound 185d

Compounds 185c and 1b(i) were reacted by a procedure analogous to that used for the synthesis of Compound 4b to give the title Compound 185d as a white solid after silica gel chromatography (28 g) eluting the column with a stepwise gradient of  $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$  (98.9:1.0:0.1) to  $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$  (94.5:5.0:0.5), using 1% increments for MeOH and 0.1% increments for  $\text{NH}_4\text{OH}$  and trituration with  $\text{Et}_2\text{O}$  to separate the isomers.

mp 120-121°C [ $\alpha$ ]<sub>D</sub> = -5.0° (c 0.10, MeOH).

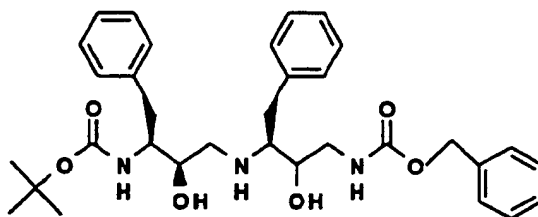
MS: (M + H)<sup>+</sup> @ 578<sup>+</sup>.

Analysis calc. for  $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_6 \cdot 0.01\text{H}_2\text{O}$ :

	C, 68.59;	H, 7.50;	N, 7.27;
Found:	C, 68.52;	H, 7.65;	N, 7.34.

Example 186

Preparation of [3S-[3R\*,2(R\*,S\*)[2S\*,3R\*)]-3-[[3-(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, phenylmethyl ester (Compound 186)



Compound 186 was prepared as a colorless solid from a 1:1 mixture of 1b(i) and 1b(ii) by a procedure analogous to that used for the synthesis of Compound 185d.

mp 90-95°C; [ $\alpha$ ]<sub>D</sub> = -4.0° (c 0.10, MeOH).

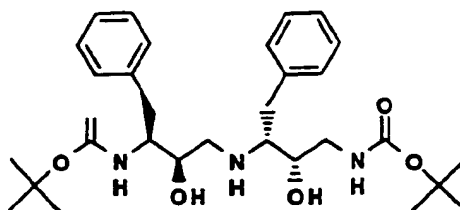
MS: (M + H)<sup>+</sup> @ 578<sup>+</sup>

Analysis calc. for  $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_6 \cdot 0.96\text{H}_2\text{O}$ :

	C, 68.40;	H, 7.81;	N, 7.25;
Found:	C, 68.39;	H, 7.57;	N, 7.26.

Example 187

Preparation of [2S-[2R\*,3S\*(2S\*,3R\*)]-3-[[3-[[3-(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, 1,1-dimethyl thyl ester (Compound 187)



Compound 187 was obtained as a white solid from the (S)-hydroxyl diastereomer of Compound 185d by removing the Cbz group using reaction conditions analogous to those used for the synthesis of Compound 7 and putting on the Boc group using a procedure analogous to that used for the synthesis of Compound 20 (CH<sub>2</sub>Cl<sub>2</sub>/DMF used as solvent).

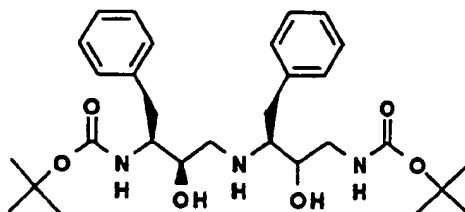
m.p. 143°C - 144°C; [α]<sub>D</sub> = -4.0° (c = 0.09, MeOH)

Elemental Analysis (%) C <sub>33</sub> H <sub>48</sub> N <sub>3</sub> O <sub>8</sub> , calculated for 0.44 H <sub>2</sub> O		
	Calc.	Found
C	65.31	65.09
H	8.38	8.22
N	7.62	7.83

	Calc.	Found
C	65.31	65.09
H	8.38	8.22
N	7.62	7.83

#### Example 188

Preparation of [3S-[3R\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, 1,1-dimethylethyl ester, 2:1 diastereomer mixture (Compound 188)



Compound 188 was obtained as a white solid from Compound 186 by removing the Cbz group using reaction conditions analogous to those used for the synthesis of Compound 7 and putting on the Boc group using a procedure analogous to that used for the synthesis of Compound 20 (CH<sub>2</sub>Cl<sub>2</sub>/DMF used as solvent).

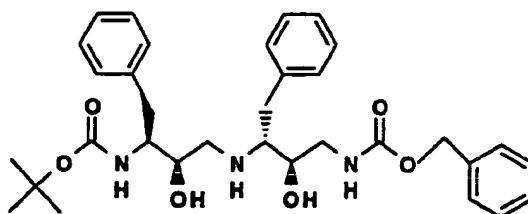
m.p. 93°C - 94°C; [α]<sub>D</sub> = +4.0° (c = 0.10, MeOH)

Elemental Analysis  
(%)  $C_{30}H_{45}N_3O_8$ , calculated for 0.2 moles  $H_2O$

	Calc.	Found
C	65.84	65.74
H	8.36	8.39
N	7.68	7.78

### Example 189

Preparation of [2R-[2R\*,3R\*(2R\*,3S\*)]]-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, phenylmethyl ester (Compound 189)



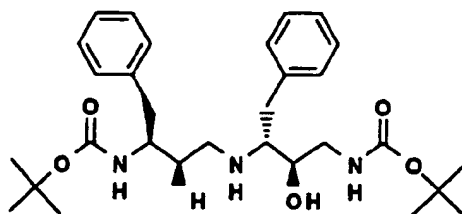
Compound 189 was obtained as a white solid from the (R)-hydroxyl diastereomer of Compound 185a by a procedure analogous to that of Example 185d.  
m.p. 112°C - 113°C;  $[\alpha]_D = +3.0^\circ$  (c = 0.09, MeOH)

Elemental Analysis  
(%)  $C_{33}H_{43}N_3O_8$ , calculated for 0.27  $H_2O$

	Calc.	Found
C	68.03	67.94
H	7.53	7.35
N	7.21	7.30

### Example 190

Preparation of [2R-[2R\*,3R\*(2R\*,3S\*)]]-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-4-phenylbutyl]carbamic acid, 1,1-dimethylethyl ester (Compound 190)



Compound 190 was obtained as a white solid from Compound 189 by a two-step procedure analogous to

that used for the synthesis of Compound 187.

m.p. 132°C - 134°C;  $[\alpha]_{\text{H}_2\text{O}} = +1.0^\circ$  (c = 0.08, MeOH)

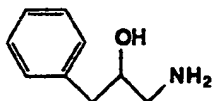
Elemental Analysis  
(%)  $\text{C}_{30}\text{H}_{45}\text{N}_3\text{O}_8$ , calculated for 1.34 moles  $\text{H}_2\text{O}$

	Calc.	Found
C	65.63	65.27
H	7.96	7.83
N	6.96	7.32

### Example 191

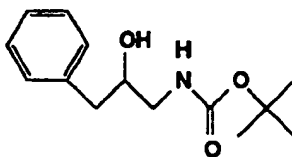
Preparation of [1S-(1R\*,2S\*)]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-2-(phenylmethyl)propyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 191e)

#### (a) Compound 191a



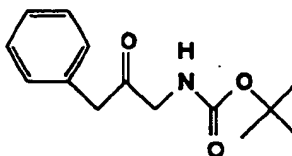
Compound 191a was prepared from epoxypropyl benzene by a procedure analogous to that used for the synthesis of Compound 16b except that  $\text{NH}_3$  saturated MeOH was used at 90°C in a sealed vessel.

#### (b) Compound 191b



Compound 191b was prepared from Compound 191a by a procedure analogous to that used for the synthesis of Compound 131 (THF/ $\text{H}_2\text{O}$  used).

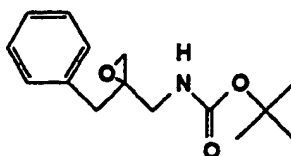
#### (c) Compound 191c



DMSO (0.17 ml, 2.40 mmol) was added to a stirred solution of  $(\text{COCl})_2$  (0.104 ml, 1.20 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5.0 ml) at -78°C. After 15 min, a solution of Compound 191b (0.10 g, 0.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (5.0 ml) was added. The reaction mixture remained at -78°C for 40 min before adding  $\text{Et}_3\text{N}$  (0.39 ml, 2.80 mmol), and warming to 0°C for 4 min. The yellow reaction mixture was then quenched with saturated  $\text{NH}_4\text{Cl}$  and the aqueous layer extracted with EtOAc. The organic layer was washed with saturated  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated

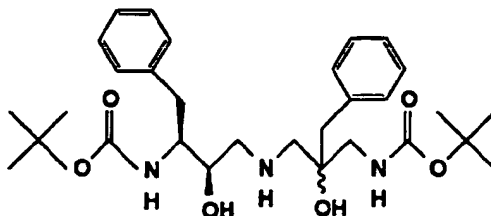
*in vacuo* to afford 0.109 g of Compound 191c as a yellow oil.

(d) Compound 191d



To a solution of Compound 191c (0.10 g, 0.40 mmol) in THF (30 ml) was added the ylide (0.60 ml, 0.962 M) freshly prepared by refluxing trimethylsulfoxonium chloride (3.75 g, 29.16 mmoles) and NaH (0.693 g, 28.88 mmol, 60% oil dispersion washed with hexane) in dry THF (30 ml) for 3.5 h. After stirring at 0°C for 75 seconds, saturated NaHCO<sub>3</sub> was added and the reaction mixture was partitioned between EtOAc and NaHCO<sub>3</sub> solution. The volatiles were evaporated to afford a yellow oil which is a mixture of Compounds 191c and 191d (1:1). The oil was dried by azeotrope with toluene three times and placing under high vacuum, then resubmitting to the reaction conditions. The isolated crude material was purified on a silica gel column (10 g), eluting the column with CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH (98.9:1.0:0.1, 97.8:2.0:0.2 and 96.7:3.0:0.3) to afford 0.69 g (66%) of Compound 191d as a yellow oil.

(e) Compound 191e

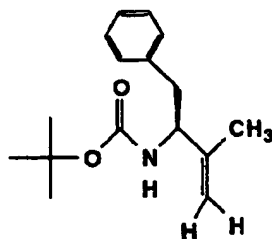


Compounds 191d and 16b were reacted by a procedure analogous to that of Example 4b (except in MeOH at 50°C) to give Compound 191e as a colorless foam.  
m.p. 65 - 67°C; [α]<sub>D</sub> = -3.0° (c 0.10, MeOH)

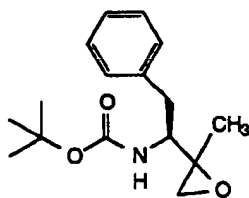
Calculated for C <sub>30</sub> H <sub>45</sub> N <sub>3</sub> O <sub>8</sub> · 0.35 H <sub>2</sub> O		
	Calc.	Found
C	65.52	65.36
H	8.37	8.42
N	7.64	7.80

Example 192

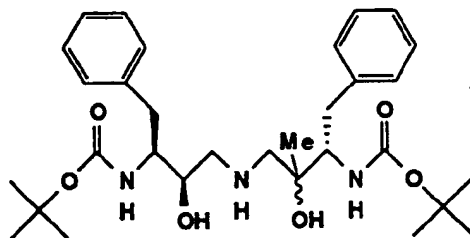
Preparation of [1S-[1R\*,2S\*(3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-2-methyl-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbamic acid, 1,1-dimethylethyl ester (Compound 192c)

(a) Compound 192a

KN(TMS)<sub>2</sub> (6.08 ml, 3.04 mmol) was added dropwise to a mixture of MePPh<sub>3</sub><sup>+</sup>Br<sup>-</sup> (1.19 g, 3.34 mmol) in toluene (8 ml) at -78°C. After 5 min, the mixture was warmed to RT and stirred for 15 min. After recooling the reaction to -78°C, a solution of 3S-3-[(1,1-dimethylethoxycarbonyl)amino]-4-phenyl-2-butanone [Godfrey et al., *Tetrahedron Letters*, **28**, 1603 (1987)] (0.40 g, 1.52 mmol) in toluene (2 ml) was added. The reaction was quenched after 35 min with pH 7 buffer and the aqueous layer extracted with EtOAc. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to afford 0.159 g of Compound 192a as a white solid (42% yield).

(b) Compound 192b

*m*-CPBA (0.13 g, 0.61 mmole) was added to a stirred solution of Compound 192a (0.16 g, 0.61 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) at 0°C. After 30 min, the reaction mixture was warmed to RT and stirred for an additional 30 min before quenching with pH 7 buffer and partitioning between aq. NaHCO<sub>3</sub> and EtOAc. The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to afford 0.17 g of a white solid. This crude material was purified by silica gel chromatography (20 g), eluting the column with 10% EtOAc/hexane to afford 0.129 g of Compound 192b as a white solid (87% yield).

(c) Compound 192c

Compounds 192b and 16b were reacted by a procedure analogous to that of Example 4b (except that the reaction was run in MeOH at 50°C) to give the title Compound 192c as a colorless foam. m.p. 63 - 66°C; [α]<sub>D</sub> = -3.0° (c 0.10, MeOH)

## Elemental Analysis (%)

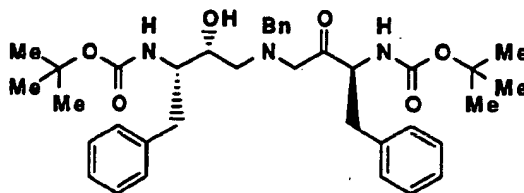
Calc. for  $C_{31}H_{47}N_3O_6 \cdot 0.42 H_2O$ 

Calc. Found

C	65.98	66.15
H	8.37	8.52
N	7.45	7.28

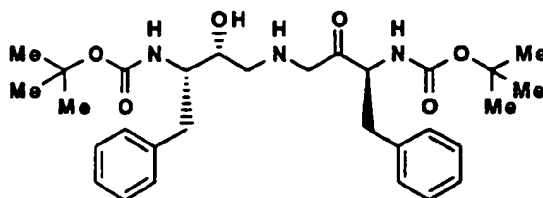
15 Example 193

Preparation of [1S-[1R\*,2S\*(3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-oxo-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 193b)

20 (a) Compound 193a

30 To a solution of Compound 1a(iii) (197 mg, 0.68 mmol), Compound 4a (250 mg, 0.66 mmol), and NaI (99 mg, 0.66 mmol) in DMF (1.8 mL) was added  $NaHCO_3$  (200 mg, 2.38 mmol). The suspension was stirred at RT for 18.5 h and then partitioned between EtOAc and  $H_2O$ . The organic extracts were dried ( $Na_2SO_4$ ) and concentrated *in vacuo* to give an oily-solid residue which was purified by flash chromatography (silica gel, 3 by 11 cm), eluting with  $MeOH:NH_4OH:CH_2Cl_2$  (0.5:0.05:99.45 and then 1:0.1:98.9) to give Compound 193a (130 mg, 31% yield) as a colorless solid.

35  $R_f$  = 0.36 (4:0.4:95.6;  $MeOH:NH_4OH:CH_2Cl_2$ ); Mass Spec. (FAB): 632 (M+H).

40 (b) Compound 193b

45 Compound 193b was prepared as a colorless solid from Compound 193a by a procedure analogous to that of Example 7 (1:1 THF:MeOH used).

m.p. dec. 116-120°C.

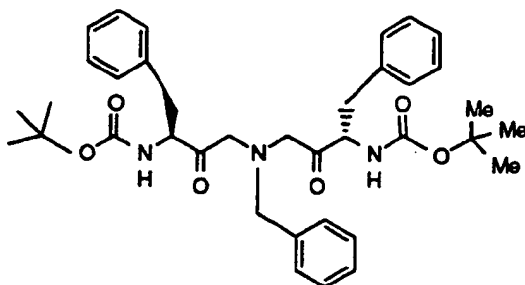
Mass Spec. (CI/ $NH_3$ ): 542 (M+H).

Anal. Calc. for $C_{30}H_{43}N_3O_6 \cdot 0.26 H_2O$ :			
	C, 65.94;	H, 8.03;	N, 7.69
Found:	C, 66.00;	H, 8.05;	N, 7.63.

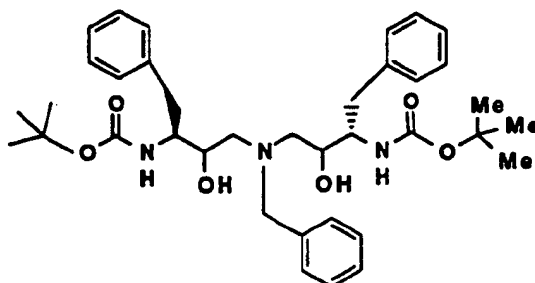


**Example 194**

Preparation of [2S-(2R\*,2R\*)]-[[[(Phenylmethyl)imino]bis[2-hydroxy-4-phenyl-3,1-butanediyl]]bis-carbamic acid, bis(1,1-dimethylethyl)ester (Compound 194b)

**(a) Compound 194a**

Compound 194a was prepared from 1 eq. of benzyl amine and 2.2 eq. of Compound 1a(iii) by a procedure analogous to that used in Example 193a.

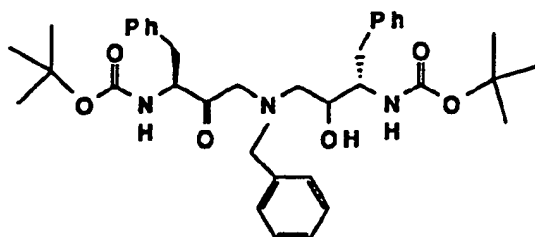
**(b) Compound 194b**

Compound 194b was prepared as a white foam from Compound 194a by a procedure analogous to that used for the synthesis of Compounds 1a(iv) and 1a(v) except that 95% EtOH was used.  
m.p. 60.0 - 62.0°C

Elemental Analysis (%) C <sub>37</sub> H <sub>51</sub> N <sub>3</sub> O <sub>8</sub>		
	Calc.	Found
C	70.11	69.67
H	8.11	8.05
N	6.63	6.43

**Example 195**

Preparation of [1S-[1R\*(3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbon yl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]-2-oxo-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 195)



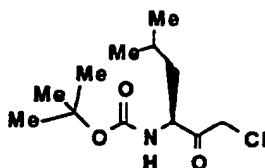
Compound 195 was also isolated as a white solid from the reaction mixture of Example 194b.  
m.p. (161.0°C softens) 176.0° - 177.0°C

Elemental Analysis (%) C <sub>37</sub> H <sub>49</sub> N <sub>3</sub> O <sub>8</sub>		
	Calc.	Found
C	70.34	69.85
H	7.82	7.86
N	6.65	6.77

#### Example 196

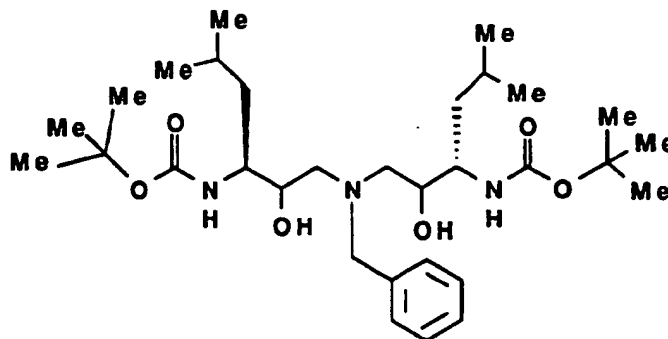
Preparation of (3S,3S')-[[[(Phenylmethyl)nitro]bis(2-hydroxy-5-methyl-3,1-hexandiyl)]biscarbamic acid, bis(1,1-dimethylethyl)ester Compound 196b)

##### (a) Compound 196a



Compound 196a was prepared from Boc-L-leucine by a procedure analogous to that used for the synthesis of Compound 1a(iii).

##### (b) Compound 196b



(diastereomers)

Compound 196b was prepared as a white foam by a two-step procedure analogous to that of Example 194b.

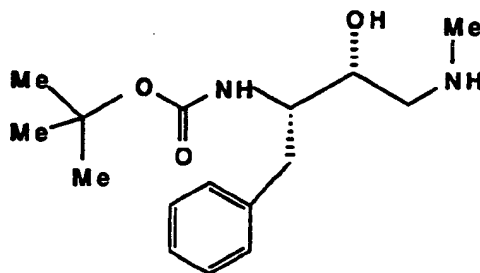
m.p. 54.0 -55.0°C

Elemental Analysis (%) $C_{31}H_{65}N_3O_8 \cdot 0.53$ $H_2O$		
	Calc.	Found
C	64.72	64.63
H	9.82	9.27
N	7.30	7.39

### Example 197

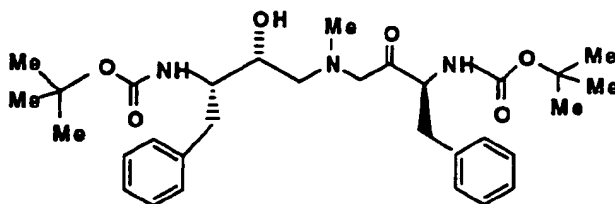
Preparation of [1S-[1R\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]-amino]-2-hydroxy-4-phenylbutyl]-methylamino]-2-oxo-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 197b)

#### (a) Compound 197a



Compound 197a was prepared from Compound 1b(i) and  $MeNH_2$  by a procedure analogous to that used for the synthesis of Compound 4a except that the reaction was run in EtOH at RT.

#### (b) Compound 197b



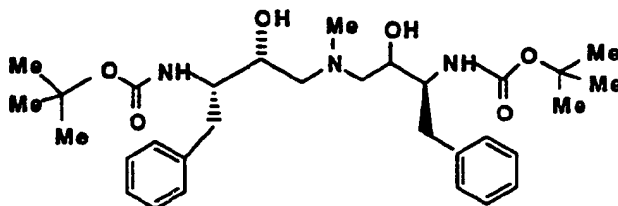
Compound 197b was prepared as a white foam from Compounds 197a and 1a(iii) by a procedure analogous to that of Example 193a.

m.p. 120.0 - 122.0°C

Elemental Analysis (%) $C_{31}H_{45}N_3O_8 \cdot 0.40$ $H_2O$		
	Calc.	Found
C	66.14	66.01
H	8.20	8.08
N	7.46	7.28

**Example 198**

Preparation of [1S-[1R\*,2S\*(3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]methylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 198)

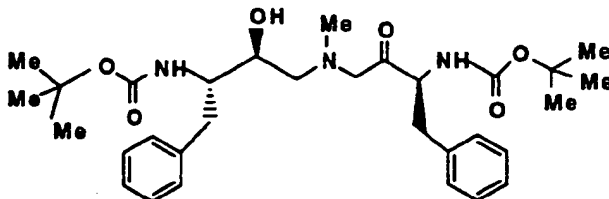


Compound 198 was prepared as a white foam from Compound 197b by a procedure analogous to that used for the synthesis of Compounds 1a(iv) and 1a(v) except that 95% EtOH was used.  
m.p. 62.0 - 70.0°C

Elemental Analysis (%) $C_{31}H_{47}N_3 \cdot 0.18$ $H_2O$		
	Calc.	Found
C	66.76	66.37
H	8.49	8.70
N	7.53	7.27

**Example 199**

Preparation of [1S-[1R\*(2R\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]methylamino]-2-oxo-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 199)



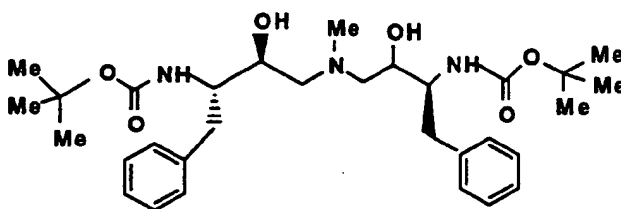
Compound 199 was prepared as a white foam from Compound 1b(ii) by a procedure analogous to that of Example 197b.

m.p. 72.0 - 80.0°C

Elemental Analysis (%) C <sub>31</sub> H <sub>45</sub> N <sub>3</sub> O <sub>8</sub>		
	Calc.	Found
C	67.00	66.84
H	8.16	8.14

**Example 200**

Preparation of [1S-[1R\*,2R\*(1R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]methylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 200)



Compound 200 was prepared as a white foam from Compound 199 by a procedure analogous to that used for the synthesis of Compounds 1a(iv) and 1a(v) except that 95% EtOH was used.  
m.p. 70.0 - 75.0°C

Elemental Analysis (%) C <sub>31</sub> H <sub>47</sub> N <sub>3</sub> O <sub>8</sub> · 0.85 H <sub>2</sub> O		
	Calc.	Found
C	64.98	65.31
H	8.57	8.30
N	7.33	7.00

**Example 201**

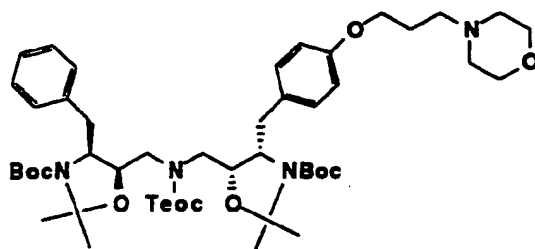
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[3-(4-morpholinyl)propoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 201d)

**(a) Compound 201a**

Ethyl-3-bromopropionate (3.20 ml; 25 mmol) was added to a mixture of morpholine (2.20 ml; 25 mmol) and Na<sub>2</sub>CO<sub>3</sub> (2.78 g; 26 mmol) in 4.5 ml of EtOH at RT. The mixture was stirred for 30 min at RT and 4 h at reflux. After cooling to RT and filtering, the filtrate was concentrated and the residue was dissolved in H<sub>2</sub>O. The pH was adjusted to ~1.5 with saturated KHSO<sub>4</sub> and the acidic mixture was washed with Et<sub>2</sub>O. Solid K<sub>2</sub>CO<sub>3</sub> was added to the aqueous layer until a pH of ~9 was reached. The basic mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>,

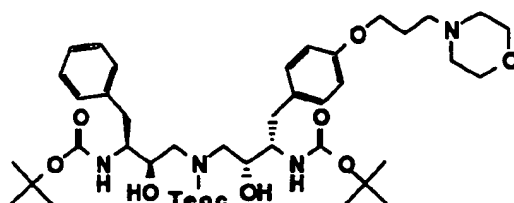
dried ( $\text{MgSO}_4$ ) and concentrated to afford 4.75 g (100+%; contain d trace solvent) of thyl-3-morpholinopropionate as a colorless liquid. A solution of this ester (935 mg; 5 mmol) in 20 ml of  $\text{Et}_2\text{O}$  was added to a suspension of  $\text{LiAlH}_4$  (400 mg; 10 mmol) in 80 ml of  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$ . After stirring for 30 min at  $0^\circ\text{C}$ , the reaction was quenched by the careful addition of 0.42 ml of  $\text{H}_2\text{O}$  followed by 0.42 ml of 15%  $\text{NaOH}$  and 1.26 ml of  $\text{H}_2\text{O}$ .  $\text{MgSO}_4$  was added and the suspension was filtered and concentrated to afford 531 mg (73%) of Compound 201a as a colorless liquid.

(b) Compound 201b



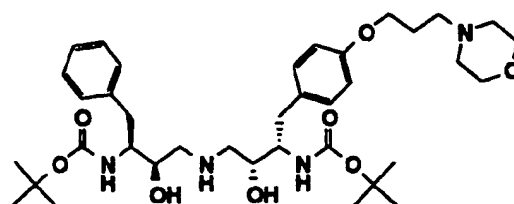
Compounds 172 and 201a were reacted by a method analogous to that described in Example 176 to give Compound 201b.

(c) Compound 201c



Compound 201b was converted into Compound 201c (white foam) by the method described for Compound 177.

(d) Compound 201d



Compound 201c was converted to the title Compound 201d (white solid) by the method described in Example 21.

mp  $122-124^\circ\text{C}$ ;  $[\alpha]_D = -4.7^\circ$  (c 0.30, MeOH).

Mass Spec. FAB + ions:  $M+H = 687$ .

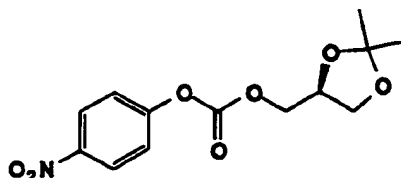
Analysis calc. for  $\text{C}_{37}\text{H}_{58}\text{N}_4\text{O}_8 \cdot 0.39\text{H}_2\text{O}$ :

	C, 64.05;	H, 8.54;	N, 8.07;
Found:	C, 64.10;	H, 8.50;	N, 8.02.

## Example 202

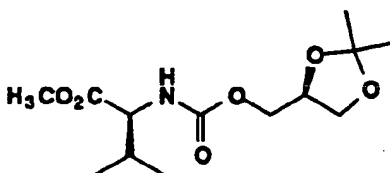
Preparation of  $[[1R^*, 2S^*(2S^*, 3R^*)], N^2-(R^*)]-N^2-[(2,3\text{-Dihydroxypropoxy})\text{carbonyl}]-N-[3-[[3-[(1,1\text{-dimethylethoxy})\text{carbonyl}]\text{amino}]-2\text{-hydroxy-4-phenylbutyl}]\text{amino}]-2\text{-hydroxy-1-(phenylmethyl)propyl}]-L\text{-valinamid}$  (Compound 202)

## (a) Compound 202a



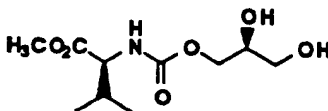
(R)-2,2-Dimethyl-1,3-dioxolane-4-methanol was converted to Compound 202a (pale yellow oil) by a method analogous to that of Example 161d.

## (b) Compound 202b



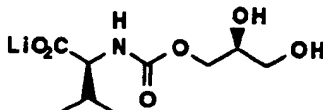
Compound 202a and valine methyl ester hydrochloride were reacted by a method analogous to that described for Example 161e to give Compound 202b (yellow oil).

## (c) Compound 202c

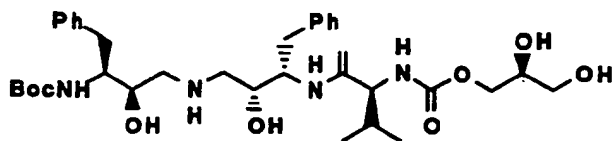


Crude Compound 202b was dissolved in a solution of glacial HOAc (10 mL) and H<sub>2</sub>O (2.50 mL) and heated at 40°-45°C in an oil bath for 3 h. Volatiles were removed *in vacuo* to afford an orange oil, which was chromatographed on silica gel (100 mL) using a gradient from 1:1 hexane:EtOAc to 100% EtOAc as eluent to afford Compound 202c (0.552 g, 74% over 2 steps) as a pale yellow oil.

## (d) Compound 202d



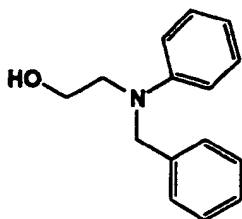
Compound 202c was converted to Compound 202d (white solid) by a method analogous to that used for the preparation of Compound 70c (THF used as solvent).



Observed  $(M + H)^+ = 661.3798 \Delta = 2.3 \text{ ppm}$

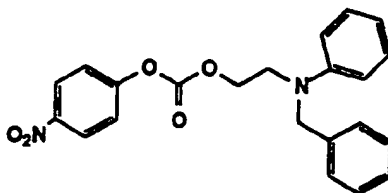
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[[2-(phenylamino)ethoxy]carbonyl]-L-valinamide (Compound 203e)

**(a) Compound 203a**



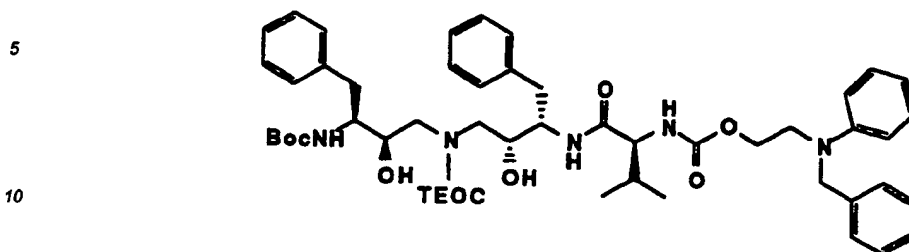
2-Anilinoethanol, benzaldehyde and NaCNBH<sub>3</sub> were reacted by a method analogous to that of Example 126 (MeOH/1% HOAc used) to give Compound 203a (clear oil).

**(b) Compound 203b**

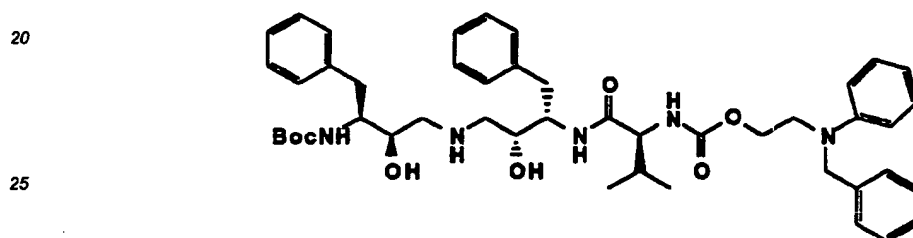


196

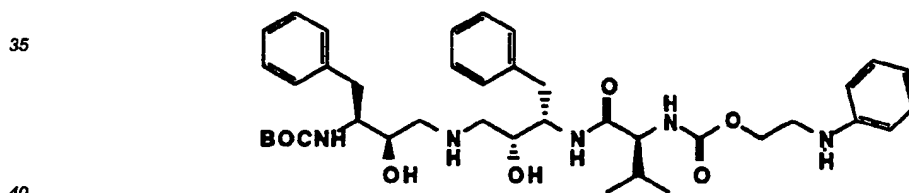


(c) Compound 203c

15 Compounds 203b and 61 were reacted by a method analogous to that described in Example 161e to give 238 mg of Compound 203c (white solid).

(d) Compound 203d

30 Compound 203c was converted into Compound 203d (white solid) by a method analogous to that described in Example 21.

(e) Compound 203e

Compound 203d was converted into the title Compound 203e (white solid) by a method analogous to that of Example 2.

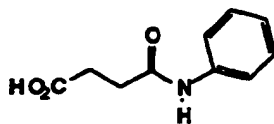
mp 162-167°C ("softening" at 150-162°C);  $[\alpha]_D = -15.5^\circ$  (c=0.69, MeOH)

45 Mass spectrum (FAB): 706 (M+H<sup>+</sup>)

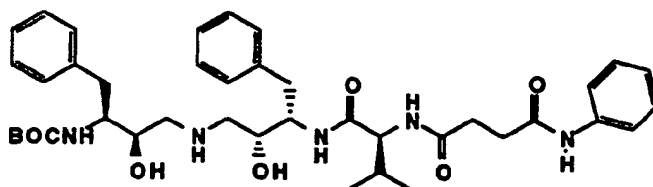
Analysis calculated for C <sub>39</sub> H <sub>55</sub> O <sub>7</sub> N <sub>5</sub> · 1.85H <sub>2</sub> O:			
	C, 63.37	H, 8.00	N, 9.47
Found:	C, 63.32	H, 7.91	N, 9.52

Example 204

55 Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amin]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[[1,4-dioxo-4-(phenylamino)butyl]-L-valinamide (Compound 204b)

(a) Compound 204a

Compound 204a was prepared by a procedure analogous to that described in *Liebigs Ann. Chem.*, 306, 326 (1899).

(b) Compound 204b

Compound 204b (white solid) was prepared starting from Compounds 61 and 204a by a two-step method analogous to that used for the conversion of Compound 48 to Compound 52.

mp 218-220°C ("softening" at 210-218°C);  $[\alpha]_D = -3.7^\circ$  (c=0.47, MeOH)

mass spectrum (FAB): 718 ( $M+H^+$ );

Analysis calculated for  $C_{40}H_{55}O_7N_5 \cdot 0.94H_2O$ :

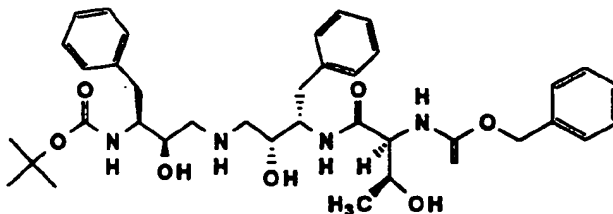
	C, 65.38	H, 7.80	N, 9.53
Found:	C, 65.44	H, 7.65	N, 9.47.

Example 205

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-allothreoninamide (Compound 205b)

(a) Preparation of Cbz-L-allothreonine (Compound 205a)

Benzylchloroformate (0.35 ml; 2.3 mmol) was added to a mixture of L-allothreonine (0.25 g; 2.1 mmol) and  $NaHCO_3$  (435 mg; 5.18 mmol) in 2.5 ml of  $H_2O$  at RT. After 3 h, the reaction mixture was partitioned between  $Et_2O$  and  $H_2O$ . The aqueous layer was washed with  $Et_2O$ , acidified to pH <2 with 6N HCl, and extracted with  $CH_2Cl_2$ . The organic layer was dried ( $MgSO_4$ ) and concentrated to afford 320 mg (63%) of Cbz-L-allothreonine.

(b) Compound 205b

Compounds 205a and 54 were reacted by a method analogous to that described in Example 55 (DMF only)

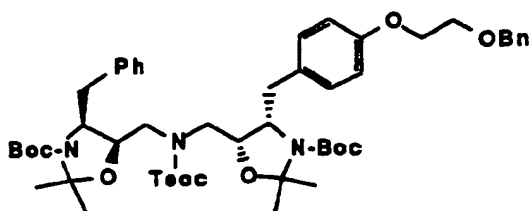
t give the title Compound 205b (white solid).  
 mp 155-157°C.;  $[\alpha]_D = 21.0^\circ$  (c 0.45, MeOH).  
 Mass Spec. FAB + ions: M+H= 679.

Analysis calc. for  $C_{37}H_{50}N_4O_8 \cdot 0.61 H_2O$ :

	C, 64.43;	H, 7.48;	N, 8.12;
Found:	C, 64.46;	H, 7.35;	N, 8.09.

#### Example 206

Preparation of [4S-[4 $\alpha$ ,5 $\alpha$ (4R\*,5S\*)]-5-[[[3-[(1,1-Dimethylethoxy)carbonyl]-4-[[4-[2-(phenylmethoxy)ethoxy]phenyl]methyl]-2,2-dimethyl-5-oxazolidinyl]methyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]methyl]-2,2-dimethyl-4-(phenylmethyl)-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester (Compound 206)

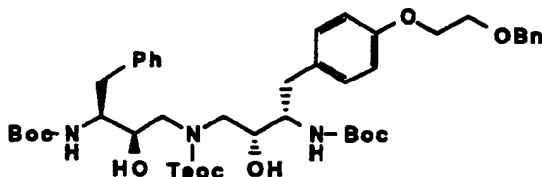


To a mixture of Compound 172 (250 mg, 0.32 mmol), 2-benzyloxyethanol (91  $\mu$ l, 0.64 mmol) and  $Ph_3P$  (167 mg, 0.64 mmol) in dry THF (0.64 ml) was added DEAD (100  $\mu$ l, 0.64 mmol). The mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (hexane/EtOAc 10:1 to 8:1) afforded 251 mg (86%) of Compound 206 as a white foam.

$^1H$  NMR (400 MHz,  $CDCl_3$ ): 7.10-7.55 (m, 12H), 6.85 (m, 2H), 4.66 (s, 2H), 4.02-4.38 (m, 8H), 3.85 (m, 2H), 3.20-3.60 (m, 4H), 2.70-3.05 (m, 4H), 1.20-1.80 (m, 30H), 0.92 (m, 2H), 0.00 (s, 9H).

#### Example 207

Preparation of [1R\*,2S\*(2S\*,3R\*)]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(phenylmethoxy)ethoxy]phenyl]butyl][[2-(trimethylsilyl)ethoxy]carbonyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamic acid, 1,1-dimethylethyl ester (Compound 207)

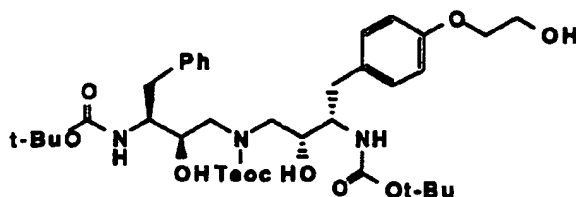


To Compound 206 (251 mg, 0.274 mmol) was added pre-cooled (10°C) 96% formic acid (6.0 ml). The mixture was stirred at 5°C for 20 min and then frozen (dry ice-acetone) and lyophilized (overnight). The residue was taken into MeOH (5 ml). To this solution was added  $Et_3N$  (115  $\mu$ l, 0.822 mmol), followed by di-*tert*-butyl-dicarbonate (60 mg, 0.274 mmol). The mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (100%  $CHCl_3$  to  $CHCl_3$ -MeOH- $NH_4OH$ : 95:5:0.5) afforded 219 mg (97%) of Compound 207 as a white foam.

$^1H$  NMR (400 MHz,  $CD_3OD$ ): 7.05-7.35 (m, 12H), 6.79 (d, J = 8.12, 2H), 4.55 (s, 2H), 4.12 (m, 2H), 4.06 (t, J = 4.70, 2H), 3.75 (t, J = 4.70, 2H), 3.54-3.85 (m, 6H), 3.10-3.30 (m, 2H, N- $CH_2$ ), 2.54 and 3.00 (both m, 4H), 1.25 and 1.26 (both s, 18H), 0.99 (m, 2H), 0.00 (s, 9H).

**Example 208**

Preparation of [1R\*,2S\*(2S\*,3R\*)]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 208)



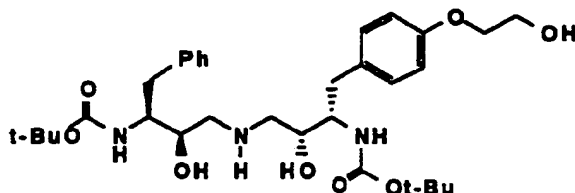
To a solution of Compound 207 (219 mg, 0.265 mmol) in 4.0 ml of MeOH was added 75 mg Pd(OH)<sub>2</sub>.

The mixture was stirred under a H<sub>2</sub> atmosphere overnight. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give 195 mg of Compound 208 as a colorless oil, which was used immediately for the next Example.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): 7.05-7.25 (m, 7H), 6.79 (d, J = 7.69, 2H), 4.12 (m, 2H), 3.95 (t, J = 4.91, 2H), 3.79 (t, J = 4.91, 2H), 3.50-3.80 (m, 6H), 3.10-3.32 (m, 2H), 2.52 and 3.00 (both m, 4H), 1.25 and 1.27 (both s, 18H), 0.99 (t, J = 8.55, 2H), 0.00 (s, 9H).

**Example 209**

Preparation of [1S-(1R\*,2S\*(2S\*,3R\*))]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 209)



A mixture of Compound 208 (195 mg, 0.265 mmol) and solid *n*-Bu<sub>4</sub>NF·nH<sub>2</sub>O (208 mg, 0.795 mmol) in dry THF (1.2 ml) was heated at 50°C for 4.0 h. After cooling to RT, Celite (1.0 g) was added and the solvent was removed under reduced pressure. Flash chromatography (100% CHCl<sub>3</sub> to CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH: 94:6:0.6) on silica gel afforded 122 mg (76%) of Compound 209 as a white solid.

M.P.: 152-154°C; [α]<sub>D</sub> = 2.9° (c 0.49, MeOH).

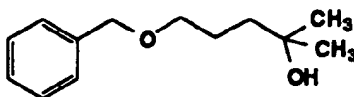
MS (FAB): 604<sup>+</sup> (M+H)<sup>+</sup>.

Anal. Calc. for C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>8</sub>·1.16H<sub>2</sub>O:

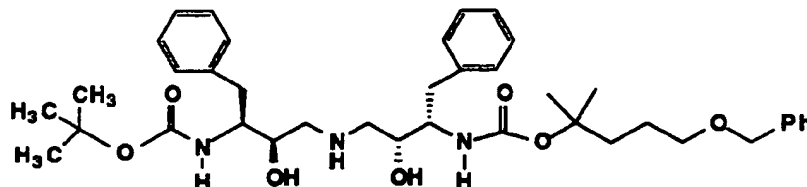
	C, 61.52;	H, 8.28;	N, 6.73.
Found:	C, 61.44;	H, 7.90;	N, 6.81.

**Example 210**

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-4-(phenylmethyl)-1,1-dimethylbutyl ester (Compound 210b)

(a) Compound 210a

Compound 210a (viscous oil) was prepared from 5-benzyloxy-2-pentanone (Jiang *et al.*, *J. Org. Chem.*, 48, 2001 (1983)) by a procedure analogous to that described in Example 158a.

(b) Compound 210b

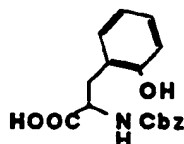
Compound 210a was converted into Compound 210b (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF used in the coupling of the p-nitrophenyl carbonate with Compound 48).

mp 139-142°C ("shrinkage" at 120-135°C);  $[\alpha]_D = -3.4^\circ$  (c 0.23, CH<sub>3</sub>OH).

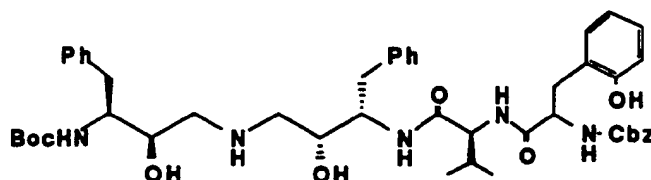
Mass Spec. (High Res.) (M+H)<sup>+</sup> = 678.4092 ( $\Delta_{\text{ppm}}$  = 3.8)

Example 211

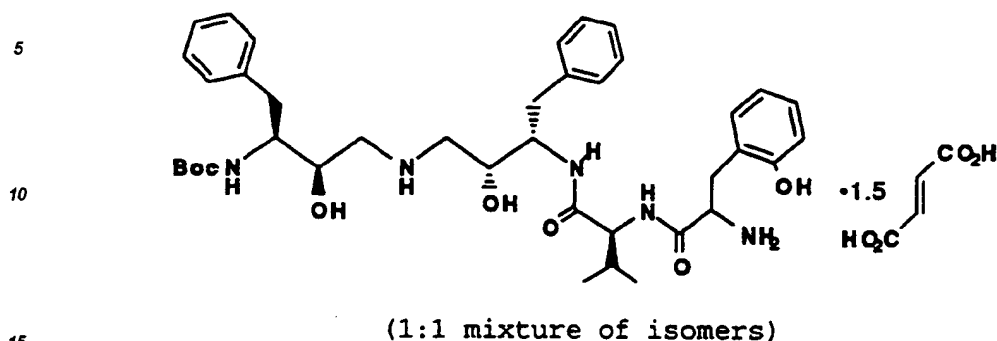
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-hydroxyphenylalanyl)-L-valinamide, fumarate (2:3) salt (Compound 211c)

(a) Compound 211a

DL- $\alpha$ -Tyrosine was converted to Compound 211a (colorless solid) by a method analogous to that described in Example 85a.

(b) Compound 211b

Comp ounds 211a and 61 were converted to Compound 211b (colorless solid) by a two-step procedure analogous to that used for th conversion f Compound 48 to Compound 52.

(c) Compound 211c

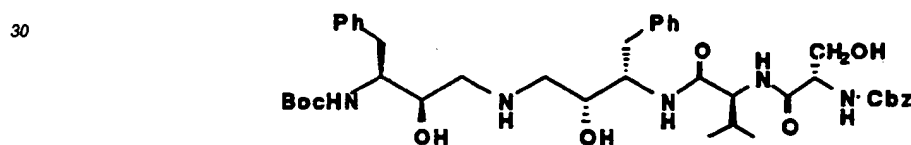
Compound 211b was converted into Compound 211c (colorless solid) by a method analogous to that described in Example 84.

High Res. Mass Spec. (FAB):  $C_{39}H_{58}N_5O_7(M+H)^+ = 706.4180^+$   $\Delta = 3.7$  ppm.

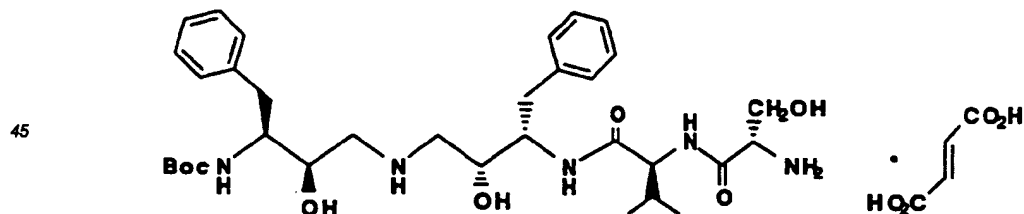
$[\alpha]_D = -12^\circ$  (c = 0.2, MeOH).

Example 212

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valyl]-L-serinamide, fumarate (2:3) salt (Compound 212b)

(a) Compound 212a

Compound 61 and N-Cbz-L-serine were converted to Compound 212a (colorless solid) by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

(b) Compound 212b

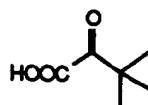
Compound 212a was converted into Compound 212b (colorless solid) by a method analogous to that described in Example 84.

m.p. 178-184°C.

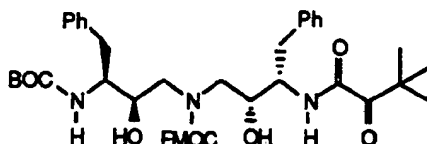
High Res. Mass Spec. (FAB):  $C_{33}H_{52}N_5O_7(M+H)^+ = 630.3850^+$   $\Delta = 2.7$  ppm.

Exempl 213

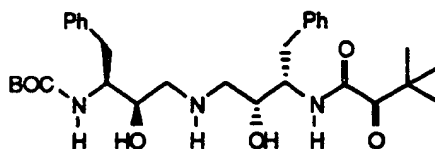
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]-[3-[[[(3,3-Dimethyl-1,2-dioxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 213c)

(a) Compound 213a

7 ml of 1 N aqueous KOH was added to 600 mg (3.8 mmoles) of t-butyl ethyl oxylate [J. Org. Chem, 35, 3726 (1970)] in 7 ml of MeOH. After 3 h, the reaction was evaporated to near dryness and the residue dissolved in H<sub>2</sub>O and washed with Et<sub>2</sub>O. The aqueous layer was acidified to pH 1, saturated with solid NaCl and extracted with Et<sub>2</sub>O. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>) and the solvent evaporated to yield a colorless oil residue. Distillation (kugelrohr, 165-175°C, 50 mm) afforded 427 mg (86% yield) of Compound 213a as a colorless oil which crystallized on standing.

(b) Compound 213b

1 eq. of HCl/MeOH was added to Compound 128 in MeOH. Filtration and evaporation gave the hydrochloride salt which was reacted with Compound 213a by a procedure analogous to that described in Example 51 to give Compound 213b as a viscous foam.

(c) Compound 213c

Compound 213b was converted to Compound 213c (white solid) by a procedure analogous to that described in Example 42.

m.p. 133-134°C;  $[\alpha]_D^{25} = -14.3^\circ$  (c 0.96, MeOH)

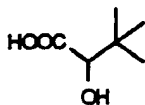
Mass Spec.: 556 (M+H)

Anal. Calc. for C<sub>31</sub>H<sub>45</sub>N<sub>3</sub>O<sub>6</sub> (555.7):

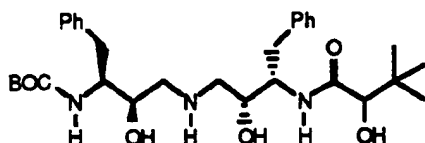
	C, 67.00;	H, 8.16;	N, 7.56.
Found:	C, 66.87;	H, 8.01;	N, 7.37.

50 Example 214

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(3,3-Dimethyl-1,2-dioxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 214b)

(a) Compound 214a

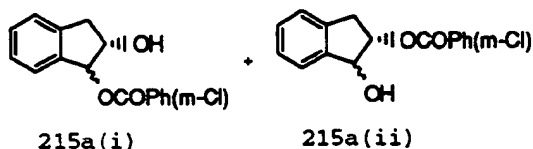
Compound 106d was converted to Compound 214a (white solid) by a procedure analogous to that described in Example 7 (EtOH used).

(b) Compound 214b

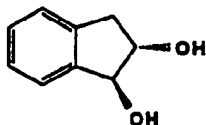
Compounds 54 and 214a were reacted by a procedure analogous to that described in Example 55 (2 eq. of N-methylmorpholine was added; DMF only used) to give the title Compound 214b (white foam). Anal. Calc. for  $C_{31}H_{47}N_3O_6 \cdot 1.75 H_2O$ : C, 63.20; H, 8.64; N, 7.13. Found: C, 63.71; H, 8.36; N, 6.62. HRMS:  $(M+H)^+ = 558.3533^+$

Example 215

Preparation of [1S-(1R\*,2S\*)](trans)-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2,3-dihydro-2-hydroxy-1H-inden-1-yl ester (Compound 215d)

(a) Compound 215a

To a solution of indene (1 ml, 8.57 mmol) in  $CH_2Cl_2$  (28 mL) was added m-CPBA (2.1 g, 9.13 mmol). After stirring for 21.5 h, the mixture was filtered and the volatiles evaporated *in vacuo*. The resulting residue was partitioned between  $CH_2Cl_2$  and saturated  $NaHCO_3$ , the aqueous layer back-extracted with  $CH_2Cl_2$ , and the combined organic layers dried ( $Na_2SO_4$ ). Evaporation *in vacuo* gave an oil containing Compounds 215a(i) and 215a(ii) (1.9 g total) which was used in the next reaction.

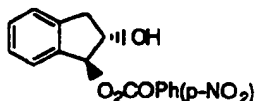
(b) Compound 215b

To a cloudy solution of crude Compounds 215a(i) and 215a(ii) (<1.9 g,  $\leq 6.89$  mmol) in MeOH (50 mL) was added NaOM (1.9 mL, 8.31 mmol, 25% in MeOH). The solution was stirred at RT for 1 h, the volatiles removed *in vacuo*, and the residue partitioned between EtOAc and brine. The combined organic layers were dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 5 by 17 cm), eluting with EtOAc: $CH_2Cl_2$  (3:2 then 2:1) to give Compound 215b (140 mg) as a colorless solid. A some-



what contaminated fraction of Compound 215b was crystallized from hot EtOAc to give a further 74 mg (214 mg, 20.7% total).

5 (c) Compound 215c

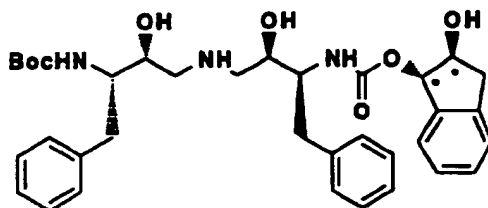


10

Compound 215b was converted to Compound 215c by a procedure analogous to that used for the synthesis of Compound 161d. Compound 215c was separated from its regioisomer by flash chromatography (silica gel, 5 x 10 cm) eluting with Et<sub>2</sub>O:pentane (1:1 then 3:2).

15

(d) Compound 215d



20

25

1:1 mixture of diastereomers at • (S,S:R,R)

30 Compounds 215c and 54 were reacted by a procedure analogous to that used in Example 147d (DMF only used) to give Compound 215d (colorless solid).

m.p. 131-133°C; [α]<sub>D</sub> = -12.3° [c 0.20, MeOH].

MS: (CI): 620 (M+H).

35

Anal. Calc. for C <sub>36</sub> H <sub>45</sub> N <sub>3</sub> O <sub>7</sub> · 1.42 H <sub>2</sub> O:			
	C, 65.14;	H, 7.47;	N, 6.51
Found:	C, 65.22;	H, 7.10;	N, 6.43.

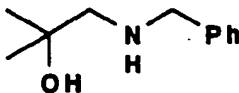
40

Example 216

Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2-amino-1,1-dimethylethyl-1,1-dimethylethyl ester (Compound 216e)

45

(a) Compound 216a



50

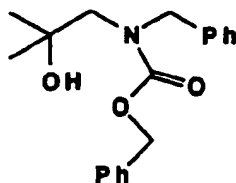
Isobutylene oxide was reacted with benzyl amine by a procedure analogous to that used in Example 4a except that MeOH at 105°C was used (sealed tube).

55

(b) Compound 216b

5

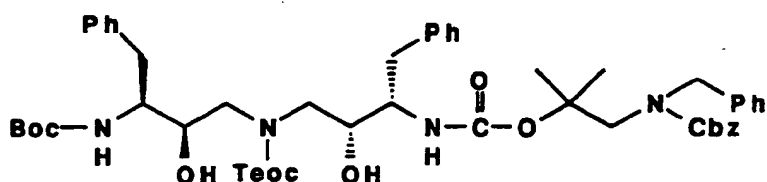
10



Compound 216a was reacted with carbobenzyloxy chloride using a procedure analogous to that of Example 122 (except that  $\text{CH}_2\text{Cl}_2$  was used and the reaction was run at RT) to give Compound 216b.

15 (c) Compound 216c

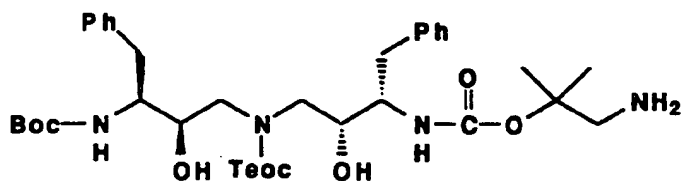
20



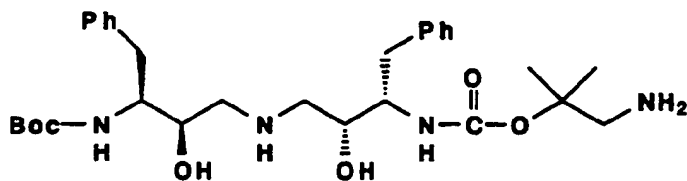
25 Compound 216b was converted to Compound 216c by a two-step procedure analogous to that used for the conversion of Compound 149c to 149e (DMF was used in coupling of p-nitrophenyl carbonate to Compound 48).

30 (d) Compound 216d

35



40 Compound 216c was converted to Compound 216d by a procedure analogous to that of Example 54.

45 (e) Compound 216e

50

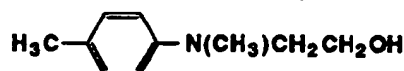
Compound 216d was converted to the title Compound 216e (white solid) by a procedure analogous to that of Example 21.  
m.p. 118-120°C.

55

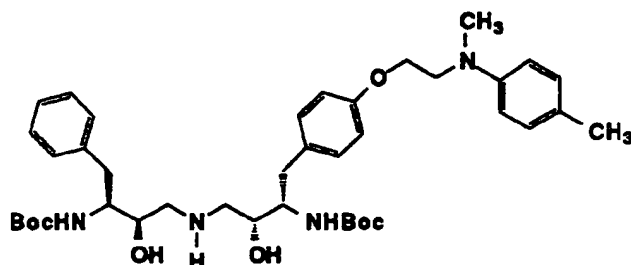
Analysis calculated for: C <sub>30</sub> H <sub>46</sub> N <sub>4</sub> O <sub>8</sub> · 1.12 H <sub>2</sub> O			
	C, 62.24;	H, 8.40;	N, 9.68.
F und:	C, 62.65;	H, 8.19;	N, 9.27.

**Example 217**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-[methyl(4-methylphen-yl)amino]ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 217b)

(a) **Compound 217a**

A mixture of N-methyl-p-toluidine (3.5 g; 29 mmol) and ethylene carbonate (4 g) was heated to 100°C for 3 h and 150°C for 10 h. After cooling to 0°C, 15 ml of 4N HCl was added and the resulting mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 4N HCl. After adjusting the pH of the aqueous layer to ~9 with solid K<sub>2</sub>CO<sub>3</sub>, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>) and concentrated to dryness. The residue was chromatographed on a 5 x 20 cm silica gel column, using 25% EtOAc/Hex as the mobile phase to afford 2.63 g (55%) of Compound 217a as a light yellow liquid.

(b) **Compound 217b**

Compound 217a and Compound 172 were reacted by a four-step procedure analogous to that used for the conversion of Compound 172 to Compound 178 to give the title Compound 217b (white solid).  
mp 120-127 °C; [α]<sub>D</sub><sup>20</sup> = -5.6° (c 0.27, MeOH).  
Mass Spec. FAB + ions: M+H = 707

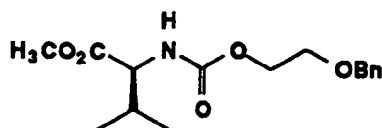
Analysis calc. for C <sub>40</sub> H <sub>58</sub> N <sub>4</sub> O <sub>7</sub> · 1.27 H <sub>2</sub> O:			
	C, 65.83;	H, 8.36;	N, 7.68;
Found:	C, 66.05;	H, 8.09;	N, 7.46.

**Example 218**

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(2-hydroxyethoxy)carbonyl]-L-valinamide (Compound 218c)

(a) Compound 218a

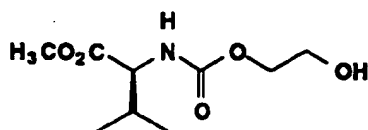
5



10 Benzyloxyethanol and valine methyl ester hydrochloride were converted to Compound 218a by a two-step procedure analogous to that used for the conversion of Compound 161c to Compound 161e.

(b) Compound 218b

15

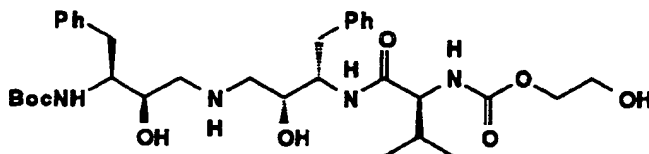


20

Compound 218a was converted to Compound 218b by a procedure analogous to that of Example 2.

(c) Compound 218c

25



30

Compounds 218b and 54 were converted to the title Compound 218c (white solid) by a two-step procedure analogous to that used for the conversion of Compound 202c to Compound 202e.

35 m.p. = 174°-179°C;  $[\alpha]_D = -16.1^\circ$  (c = 0.23; MeOH) High resolution MS (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>33</sub>H<sub>51</sub>N<sub>4</sub>O<sub>8</sub>) = 631.3707;

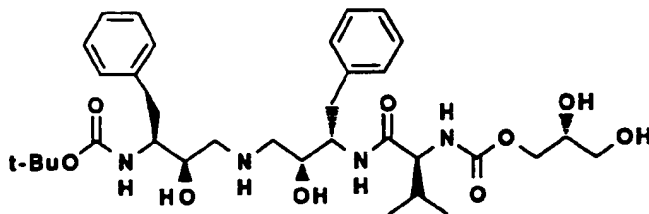
Observed (M + H)<sup>+</sup> = 631.3709 Δ = 0.3 ppm

Example 219

40

Preparation of [(1R\*,2S\*(2S\*,3R\*))]-N<sup>2</sup>-(S\*)]-N<sup>2</sup>-(2,3-Dihydroxypropoxy)carbonyl]-N-[3-[(1,1-dimethylethoxy)carbonyl]-amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 219)

45



50

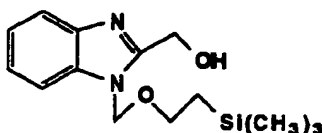
55 Starting from (S)-(+)-2,2 dimethyl-1,3-dioxolane-4-methanol, the title Compound 219 (white solid) was prepared by a procedure analogous to that used for the preparation of Compound 202e. m.p. = 200°-205°C (decomposes);  $[\alpha]_D = -3.3^\circ$  (c = 0.30; MeOH).

High resolution MS (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>34</sub>H<sub>53</sub>O<sub>9</sub>N<sub>4</sub>) = 661.3831;

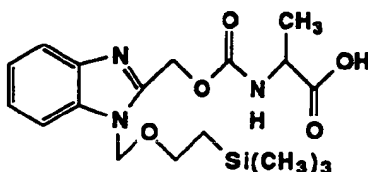
Observed (M + H)<sup>+</sup> = 661.3798 Δ = 2.3 ppm

**Example 220**

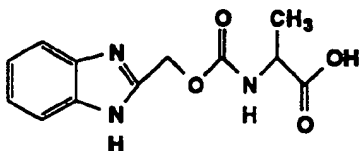
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N2-[[2-Benzimidazolyl)methoxy]carbonyl]-N-[3-[[3-[[1,1-dimethylthoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-alaninamid (Compound 220d)

**(a) Compound 220a**

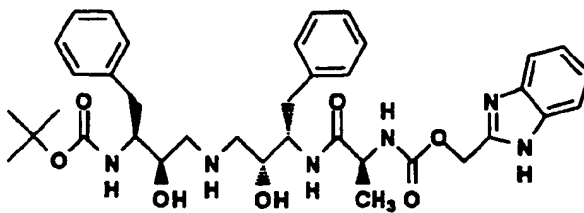
Compound 93a and 2-(trimethylsilyl)ethoxymethyl chloride was converted to Compound 220a by a procedure analogous to that of Example 93b (reaction was run at 70°C).

**(b) Compound 220b**

Compound 220a and alanine were reacted by a two-step procedure analogous to that used for the conversion of Compound 93b to Compound 93d to give Compound 220b.

**(c) Compound 220c**

Compound 220b in a 4M HCl/dioxane solution (23ml) was stirred at 50°C for 2.5 h then cooled to RT and stirred overnight. The reaction was concentrated and the resulting yellow foam was purified by silica gel chromatography, eluting the column with a stepwise gradient of EtOAc, EtOAc:AcOH (98:2), and EtOAc:MeOH:AcOH (78:20:2) to afford 0.498 g (70%) of Compound 220c.

**(d) Compound 220d**

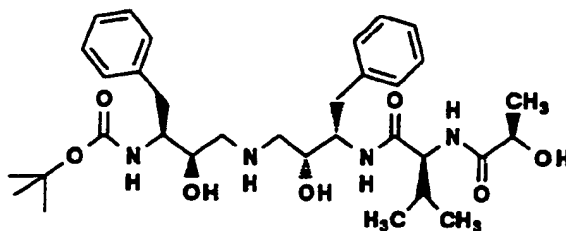
Compounds 220c and 54 were reacted by a procedure analogous to that used for the preparation of Compound 93f to give the title Compound 220d (white solid).

m.p. 106-108°C;  $[\alpha]_D^{25} = -1.0^\circ$  (c, 0.10 M OH). Mass Spec. FAB: (M + H)<sup>+</sup> @ 689<sup>+</sup>.

Analysis calc. for $C_{37}H_{46}N_8O_7 \cdot 0.65H_2O$ :			
	C, 63.63;	H, 6.83;	N, 12.03;
F und:	C, 63.66;	H, 7.13;	N, 11.99.

**Example 221**

Preparation of [1S-[[[1R\*,2S\*(2S\*,3R\*)],N<sup>2</sup>-(S\*)]]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-hydroxy-1-oxopropyl)-L-valinamide (Compound 221)



Compound 61 and D-lactic acid were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52 to give the title Compound 221 (white solid).

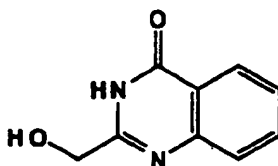
mp 213-219°C;  $[\alpha]_D = -56.8^\circ$  (c 0.19, AcOH).

Mass Spec. FAB+ ion: M+H= 615.

Analysis calc. for $C_{33}H_{50}N_4O_8 \cdot 1.34 H_2O$ :			
	C, 62.04;	H, 8.31;	N, 8.77;
Found:	C, 62.02;	H, 7.87;	N, 8.79.

**Example 222**

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[[[(3,4-Dihydro-4-oxo-2-quinazolinyl)methoxy]carbonyl]-N-[3-[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 222d)

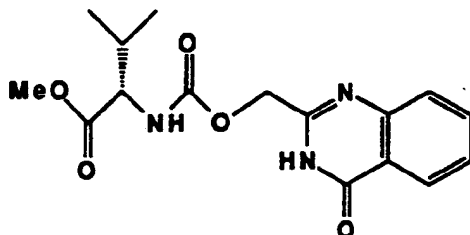
**(a) Compound 222a**

Compound 222a was prepared according to the procedure of Bergman et al., *Tetrahedron*, 46, 1296 (1990).

(b) Compound 222b

5

10

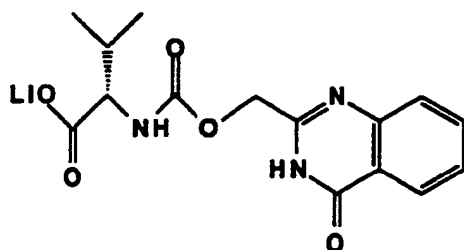


15 Compound 222a and L-valine methyl ester hydrochloride were reacted by a two-step procedure analogous to that used for the conversion of Compound 161c to Compound 161e to give Compound 222b.

(c) Compound 222c

20

25



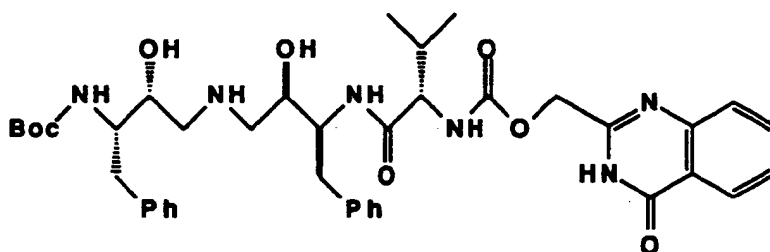
30 Compound 222b was converted to Compound 222c by a procedure analogous to that of Example 70c.

30

(d) Compound 222d

35

40



45 Compounds 222c and 48 were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52 (no N-methylmorpholine was used in the EDCI coupling step) to give the title Compound 222d (white solid).

m. p. 105-107°C.  $[\alpha]_D^{25} = +1.8^\circ$  (c = 0.5, MeOH).

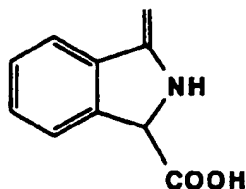
High Res Mass Spectrum:  $(M+H)^+ = 745.3925$ , theoretical:  $(M+H)^+ = 745.3925$  ( $\Delta$  0.0 ppm error).

Example 223

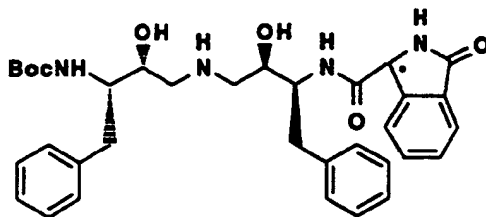
50

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(2,3-Dihydro-3-oxo-1H-indolizin-1-yl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 223b)

55

(a) Compound 223a

To a MeOH (50 mL) solution of 2-carboxybenzaldehyde (5.0 g, 0.033 mol) in a cool water bath ( $\sim 18^\circ\text{C}$ ) was added  $\text{NH}_3$  gas for 15 min, and the solution stirred at RT for 1 h. Aqueous NaCN (1.63 g, 0.033 mol in 50 mL  $\text{H}_2\text{O}$ ) was then added dropwise over 15 min. After 1 h, the volatiles were concentrated *in vacuo* and the resulting yellow solution was treated with 6N HCl (40 mL). A precipitate formed after several mls of HCl had been added and the reaction slowly became homogeneous. The reaction mixture was heated at  $100^\circ\text{C}$  for 1.45 h, then placed in a cool water bath ( $\sim 18^\circ\text{C}$ ). A yellow solid quickly formed and was removed by filtration, washing with  $\text{H}_2\text{O}$  and acetone. The filtrate was allowed to stand at RT for several days and the resulting solid was collected by filtration, washing with  $\text{H}_2\text{O}$  and acetone to give slightly impure Compound 223a (2.2 g,  $\sim 38\%$  yield). A portion (670 mg) of this material was crystallized from hot  $\text{H}_2\text{O}$ , washing the solid with more  $\text{H}_2\text{O}$  and drying *in vacuo* to give Compound 223a (359 mg) as a colorless solid.

(b) Compound 223b

(1:1 mixture of diastereomers at •)

Compounds 223a and 54 were reacted by a procedure analogous to that of Example 93f to give the title Compound 223b (colorless solid).

m.p. dec.  $141\text{--}152^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25} = -1.2^\circ$  (c 0.16, AcOH).

MS: (FAB): 603 (M+H).

Anal. Calc. for $\text{C}_{34}\text{H}_{42}\text{N}_4\text{O}_6 \cdot 0.82 \text{ H}_2\text{O}$ :			
	C, 66.14;	H, 7.12;	N, 9.07
Found:	C, 66.10;	H, 6.88;	N, 9.11.

Example 224

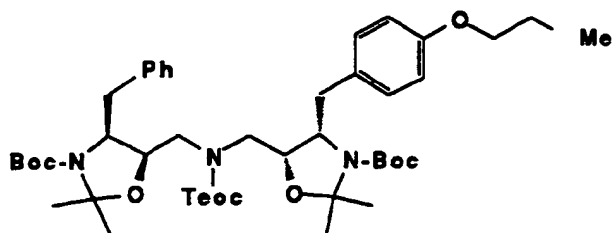
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-methoxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 224c)



(a) Compound 224a

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10

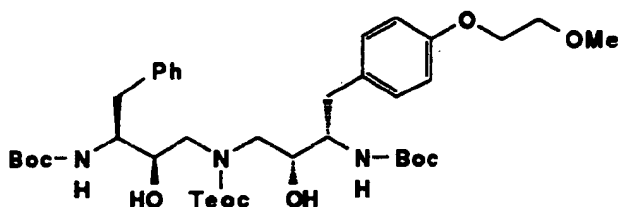


15 To a mixture of Compound 172 (250 mg, 0.32 mmol), 2-methoxyethanol (50  $\mu$ l, 0.64 mmol) and  $\text{PPh}_3$  (167 mg, 0.64 mmol) in dry THF (0.64 ml) was added DEAD (100  $\mu$ l, 0.64 mmol). The mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (hexane/EtOAc 10:1 to 7:1) afforded 225 mg (84%) of Compound 224a as a white foam.

(b) Compound 224b

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25



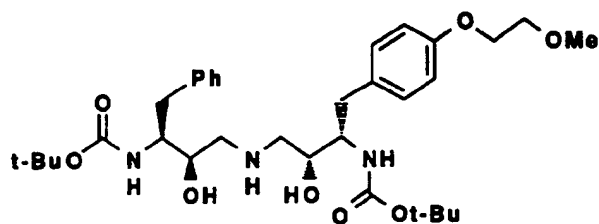
30 To Compound 224a (225 mg, 0.267 mmol) was added pre-cooled (10°C) 96% formic acid (5.0 ml). The mixture was stirred at 5°C for 20 min and was then frozen (dry ice-acetone) and lyophilized (overnight). The residue was taken into MeOH (5 ml) and  $\text{Et}_3\text{N}$  (112  $\mu$ l, 0.80 mmol) was added followed by di-*tert*-butyldicarbonate (88 mg, 0.40 mmol). The mixture was stirred at RT overnight. Concentration *in vacuo* followed by flash chromatography (100%  $\text{CHCl}_3$  to  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 96:4:0.4) afforded 203 mg (100%) of Compound 224b as a white foam.

35

(c) Compound 224c

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50 A mixture of Compound 224b (203 mg, 0.27 mmol) and solid  $n\text{-Bu}_4\text{NF}\cdot n\text{H}_2\text{O}$  (223 mg, 0.85 mmol) in dry THF (1.3 ml) was heated at 50°C for 4.0 h. After cooling to RT, Celite (1.0 g) was added and the solvent was removed under reduced pressure. Flash chromatography (100%  $\text{CHCl}_3$  to  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 94:6:0.6) on silica gel afforded 128 mg (73%) of the title Compound 224c as a gel, which upon trituration with  $\text{Et}_2\text{O}$ -hexane afforded the product as a white solid.

m.p.: 136-138°C;  $[\alpha]_D = -2.3^\circ$ ,  $[\alpha]_{H_9}(436) = -6.1^\circ$ ,  $[\alpha]_{H_9}(365) = -14.2^\circ$ , (c 0.53, MeOH).

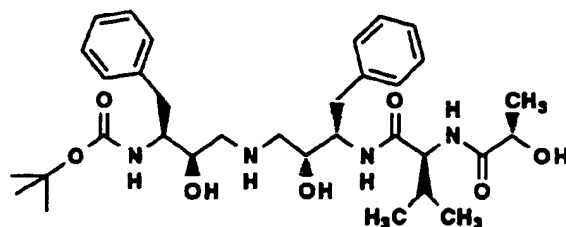
Mass Spec. (FAB): 618<sup>+</sup> (M+H)<sup>+</sup>.

55 Anal. Calc. for  $\text{C}_{33}\text{H}_{51}\text{N}_3\text{O}_8\cdot 0.83\text{H}_2\text{O}$ : C, 62.65; H, 8.39; N, 6.64. Found: C, 62.52; H, 8.12; N, 6.77.

Exmpl 225

Preparation of [1S-[1R\*,2S\*(2S\*(2S\*,3R\*))],N<sup>2</sup>-(R\*)]-N-[3-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hy-

droxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-hydroxy-1-oxo-propyl)-L-valinamid  
(Compound 225)



Compound 61 and L-lactic acid were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52 to give the title Compound 225 (white solid).  
m.p. 210-214°C;  $[\alpha]_D = -24.8^\circ$  (c 0.31, MeOH).  
Mass Spec. (FAB+ ion): M+H= 615.

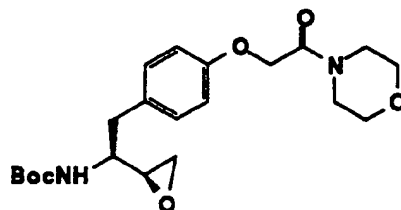
Analysis calc. for  $C_{33}H_{50}N_4O_8 \cdot 1.00 H_2O$ :

	C, 62.63;	H, 8.28;	N, 8.85;
Found:	C, 62.37;	H, 7.84;	N, 8.74.

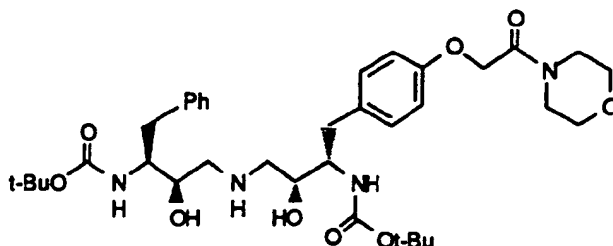
#### Example 226

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-[2-(4-morpholinyl)-2-oxo-ethoxy]phenyl)]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 226b)

##### (a) Compound 226a



NaH (48 mg, 60% dispersion in mineral oil, 1.2 mmol) was washed twice with hexane and suspended in 1.0 ml of dry DMF. The suspension was cooled to 0°C and a solution of Compound 175c (280 mg, 1.0 mmol) in 1.5 ml of dry DMF was added. The mixture was stirred at 0°C for 30 min and then 4-(2-bromoacetyl)morpholine (*J. Med. Chem.*, **35**, 1685 (1992); 270 mg, 1.3 mmol) was added in one portion, followed by n-Bu<sub>4</sub>NI (185 mg, 0.5 mmol). The resulting mixture was stirred at RT overnight. After cooling to 10°C, H<sub>2</sub>O was added and the mixture extracted with EtOAc. The combined extracts were washed with H<sub>2</sub>O and brine, dried (NaHCO<sub>3</sub>) and concentrated *in vacuo* to give a crude product which was purified by flash chromatography (hexane-EtOAc: 1:1 to 1:4) on silica gel to give 392 mg (96%) of Compound 226a as a white solid.

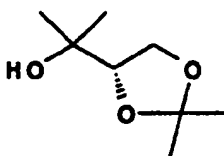
(b) Compound 226b

A mixture of Compounds 226a (407 mg, 1.0 mmol) and 16b (280 mg, 1.0 mmol) in 1.0 ml of dry DMF was heated at 100°C for 4.0 h. Concentration *in vacuo* followed by flash chromatography (CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH: 98:2:0.2 to 95:5:0.5) on silica gel afforded 501 mg (73%) of Compound 226b as a white solid. m.p. 118-120°C;  $[\alpha]_D = -4.7^\circ$ ,  $[\alpha]_{365}(\text{MeOH}) = -23.6^\circ$  (c 1.0, MeOH). Mass Spec. (FAB): 687<sup>+</sup> (M+H)<sup>+</sup>.

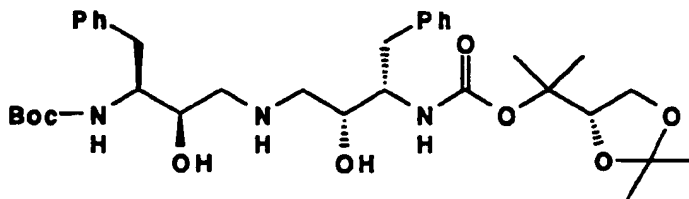
Anal. Calc. for C <sub>38</sub> H <sub>54</sub> N <sub>4</sub> O <sub>9</sub> ·0.30H <sub>2</sub> O:			
	C, 62.46;	H, 7.95;	N, 8.09.
Found:	C, 62.46;	H, 7.91;	N, 8.28.

Example 227

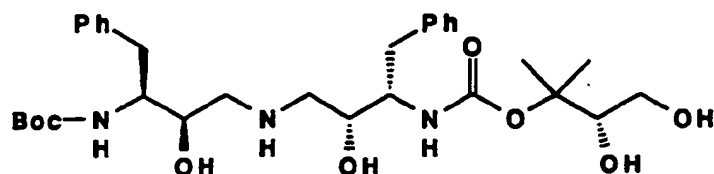
Preparation of [1S-(1R\*,2S\*), (R\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2,3-dihydroxy-1,1-dimethylpropyl 1,1-dimethylethyl ester (Compound 227c)

(a) Compound 227a

Methyl (S)-(-)-2,2-dimethyl-1,3-dioxolane-4-carboxylate was converted to Compound 227a by a procedure analogous to that of Example 158a.

(b) Compound 227b

Compound 227a was converted to Compound 227b by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used in the coupling of the p-nitrophenyl carbamate with Compound 48).

(c) Compound 227c

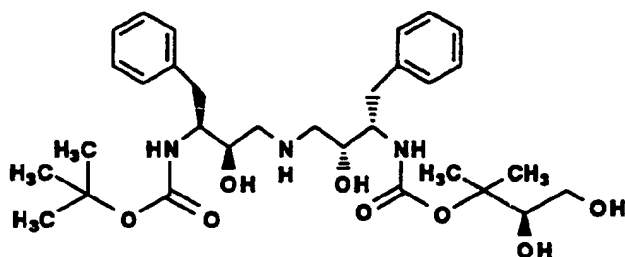
Compound 227b was converted to Compound 227c (white solid) by a procedure analogous to that of Example 202c.

m.p. 104–105°C.

High Res Mass Spectrum:  $(M+H)^+ = 590.3463$ , theoretical:  $(M+H)^+ = 590.3441$  ( $\Delta$  4 ppm error).

Example 228

Preparation of [1S-(1R\*,2S\*), (S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2,3-dihydroxy-1,1-dimethylpropyl 1,1-dimethylethyl ester (Compound 228)



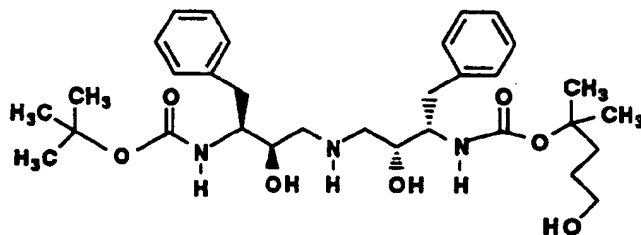
Methyl (R)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxylate was converted to the title Compound 228 (white solid) by a procedure analogous to that used for the synthesis of Compound 227c.

m.p. 69–72°C;  $[\alpha]_D = -6.0^\circ$  (c = 0.2, CD<sub>3</sub>OD)

Analysis Calculated for: C <sub>31</sub> H <sub>47</sub> N <sub>3</sub> O <sub>8</sub> · 1.03 H <sub>2</sub> O			
	C, 61.20;	H, 8.13;	N, 6.91.
Found:	C, 61.26;	H, 7.93;	N, 6.85.

Example 229

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 4-hydroxy-1,1-dimethyl-butyl 1,1-dimethylethyl ester (Compound 229)



Compound 210b was converted to the title Compound 229 (white solid) by a procedure analogous to that

of Example 2.

m.p. 80-84°C;  $[\alpha]_D = -2.6^\circ$  (c 0.2, CH<sub>3</sub>OH).

High Res Mass Spec (M + H)<sup>+</sup> = 588.3649 ( $\Delta$  ppm = 1.2)

5 Analysis calc. for C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>7</sub>·2.69H<sub>2</sub>O:

Calculated C, 60.42; H, 8.61; N, 6.60;

Found: C, 60.46; H, 8.22; N, 6.56.

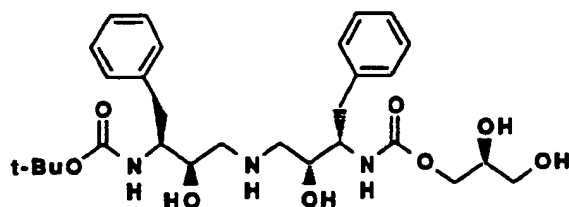
#### Example 230

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Preparation of [1S-(1R\*,2S\*), (R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2,3-dihydroxypropyl 1,1-dimethylethyl ester (Compound 230)

15

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(R)-2,2-Dimethyl-1,3-dioxolane-4-methanol was converted to the title Compound 230 (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48).

25

m.p. = 151°-154°C (decomposes);  $[\alpha]_D = -5.3^\circ$  (c = 0.30; MeOH).

High resolution MS (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>29</sub>H<sub>43</sub>N<sub>3</sub>O<sub>8</sub>) = 562.3128; Observed (M + H)<sup>+</sup> = 562.3147  $\Delta$  = 3.4 ppm

30

Analysis for C <sub>29</sub> H <sub>43</sub> N <sub>3</sub> O <sub>8</sub> ·1.31 H <sub>2</sub> O:			
Calculated:	C, 59.51;	H, 7.86;	N, 7.48
Found:	C, 59.19;	H, 7.47;	N, 7.18.

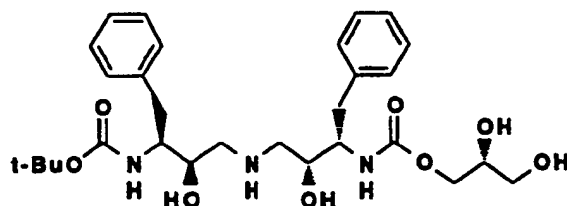
35

#### Example 231

Preparation of [1S-(1R\*,2S\*), (S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2,3-dihydroxypropyl 1,1-dimethylethyl ester (Compound 231)

40

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(S)-2,2-Dimethyl-1,3-dioxolane-4-methanol was converted to the title Compound 231 (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48).

m.p. = 157°-160°C;  $[\alpha]_D = -8.7^\circ$  (c = 0.31; MeOH)

55

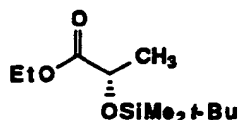
High resolution MS (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>29</sub>H<sub>44</sub>O<sub>8</sub>N<sub>3</sub>) = 562.3128; Observed (M + H)<sup>+</sup> = 562.3127;  $\Delta$  = 0.2ppm

Analysis for  $C_{29}H_{43}N_3O_8 \cdot 0.45 H_2O$ :

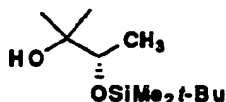
Calculated:	C, 61.13;	H, 7.77;	N, 7.38
Found:	C, 60.94;	H, 7.62;	N, 7.57

**Example 232**

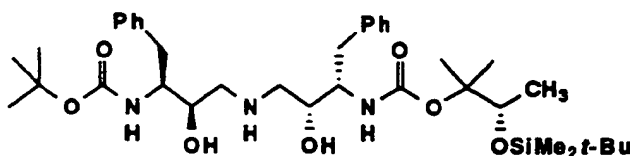
**Preparation of [1S-(1R\*,2S\*), (R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2-hydroxy-1,1-dimethylpropyl ester (Compound 232d)**

**(a) Compound 232a**

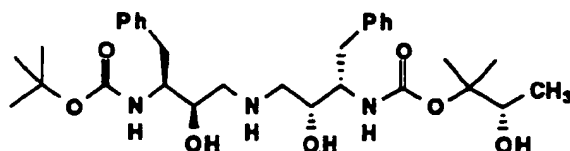
To a solution of 0.5 g (0.48 ml; 4.23 mmol) of (S)-Ethyl lactate in 8.5 ml of  $CH_2Cl_2$  at  $0^\circ C$  was added 1.13 ml (1.2 eq; 5.07 mmol) of 2,6-di-*t*-butylpyridine followed by 1.16 ml (1.2 eq; 5.07 mmol) of *t*-butyldimethylsilyl triflate. After 1 h at  $0^\circ C$ ,  $Et_2O$  and 1N HCl were added and the organic layer washed with  $H_2O$ , saturated  $NaHCO_3$ , and brine. The extracts were dried ( $MgSO_4$ ) and evaporated *in vacuo* to give a crude liquid which was purified by flash chromatography (25 mm X 7"; elution with 2%  $EtOAc$ /Hexanes then 5%  $EtOAc$ /Hexanes) to give 0.89 g (90%) of Compound 232a as a colorless liquid.

**(b) Compound 232b**

Compound 232a was converted to Compound 232b by a procedure analogous to that used in Example 149c.

**(c) Compound 232c**

Compound 232b was converted to Compound 232c by a two-step procedure analogous to that used for the conversion of Compound 147b(i) to Compound 147d.

**(d) Compound 232d**

Compound 232c was converted to Compound 232d (white solid) by a procedure analogous to that of Example 162.

m.p. 129-131°C (softens at 90°C);  $[\alpha]_D^{25} = -20.9^\circ$  (c 0.32, MeOH).

Mass Spec.: FAB + ions: M+H= 574.

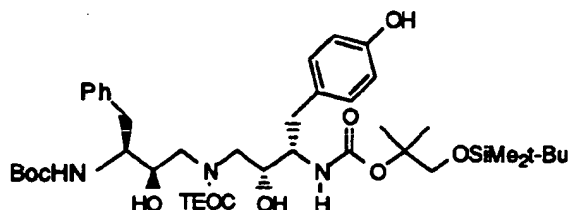
Analysis calc. for  $C_{31}H_{47}N_3O_7 \cdot 0.15 H_2O$ :

	C, 64.59;	H, 8.27;	N, 7.29;
Found:	C, 64.47;	H, 8.25;	N, 7.41.

### Example 233

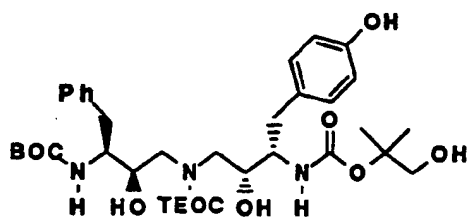
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-hydroxyphenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester (Compound 233c)

#### (a) Compound 233a



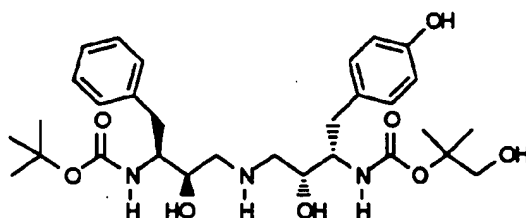
Compounds 19 and 161d were reacted by a procedure analogous to that of Example 143 (i-Pr<sub>2</sub>NEt and DMF were used) to give Compound 233a.

#### (b) Compound 233b



Compound 233a was converted to Compound 233b by a procedure analogous to that of Example 162.

#### (c) Compound 233c



Compound 233b was converted to Compound 233c (white solid) in 28% yield by a procedure analogous to that of Example 21.

m.p. 135-137°C;  $[\alpha]_D = -4.9^\circ$  (c 0.55, MeOH).

5 MS:  $(M+H)^+$  576.3290<sup>+</sup> (High resolution).

Anal. Calc for  $C_{30}H_{45}N_3O_6$ : C, 62.59; H, 7.88; N, 7.30.

Found: C, 62.20; H, 7.86; N, 7.38.

#### Example 234

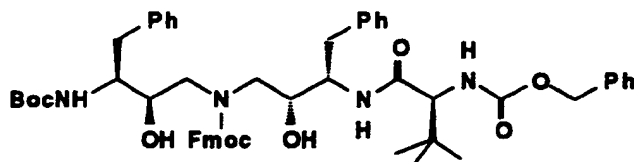
10

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*), (R\*)]]-[3-[[3-[[3,3-Dimethyl-2-(formylamino)-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 234c)

15

#### (a) Compound 234a

20



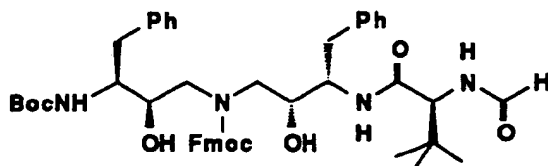
To a mixture of Compound 88b (286 mg, 0.414 mmol) and *i*-Pr<sub>2</sub>NEt (94  $\mu$ l, 0.538 mmol) in 2.5 ml of dry DMF at 0°C was added 9-fluorenylmethylchloroformate (124 mg, 0.48 mmol). The mixture was stirred at 0°C for 1.0 hr and H<sub>2</sub>O was added. The mixture was extracted with EtOAc and the extracts were washed with sat'd NaHCO<sub>3</sub> and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (hexane/EtOAc 4:1 to 1:1) on a silica gel column afforded 341 mg (90%) of Compound 234a as a white solid.

TLC(SiO<sub>2</sub>)R<sub>f</sub> = 0.51.

30 (CHCl<sub>3</sub> - MeOH 95:5 - PMA).

#### (b) Compound 234b

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A mixture of Compound 234a (341 mg, 0.374 mmol), 1,4-cyclohexadiene (356  $\mu$ l) and 10% Pd-C (40 mg) in 11 ml of EtOH was stirred under a H<sub>2</sub> atmosphere for 2 h. An additional 25 mg of 10% Pd-C was added after 2 and 4 h. After 6 h total, the catalyst was removed by filtration through a short pad of Celite. 90  $\mu$ l of HOAc was added to the filtrate and the mixture was evaporated to dryness to yield 308 mg of the amine acetate salt as a white solid.

45

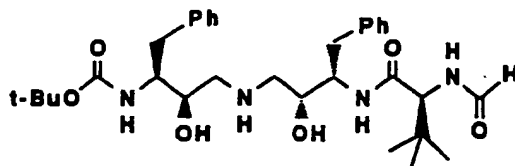
Formic acetic anhydride was prepared by addition of 46.3  $\mu$ l of HCO<sub>2</sub>H to 133  $\mu$ l of ice-cooled Ac<sub>2</sub>O. The solution was then stirred at 50°C for 2 h. This material dissolved in 1 ml of dry THF was added to an ice-cooled solution of 308 mg of the amine acetate salt in 2.5 ml of dry THF. The mixture was stirred at 0°C for 1.0 h and then at RT for 15 min. The reaction mixture was partitioned between H<sub>2</sub>O and EtOAc and the organic extracts were washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration *in vacuo* followed by purification by prep HPLC (Nova-Pak HR silica 60Å) with 60% EtOAc in hexane as eluent, afforded 123 mg (41% for two steps) of Compound 234b as a white solid.

50

TLC(SiO<sub>2</sub>)R<sub>f</sub> = 0.17.

55 (CHCl<sub>3</sub>-MeOH 95:5 - PMA).



(c) Compound 234c

To a solution of Compound 234b (123 mg, 0.152 mmol) in 2.7 ml of dry  $\text{CH}_2\text{Cl}_2$  was added piperidine (132  $\mu\text{l}$ , 1.34 mmol). The mixture was stirred at RT for 1.5 h. Concentration *in vacuo* followed by flash chromatography ( $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$ : 99:1:0.1 to 92:8:0.8) on silica gel gave, after trituration with  $\text{CHCl}_3$ -hexane, 84 mg (94%) of the title Compound 234c as a white solid.

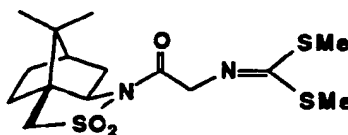
m.p.: 166-168°C;  $[\alpha]_D^{25} = 23.8^\circ$ ,  $[\alpha]_{438}^{25} = -54.8^\circ$  (c 0.21, MeOH).

Mass Spec. (FAB): 585<sup>+</sup> (M+H)<sup>+</sup>.

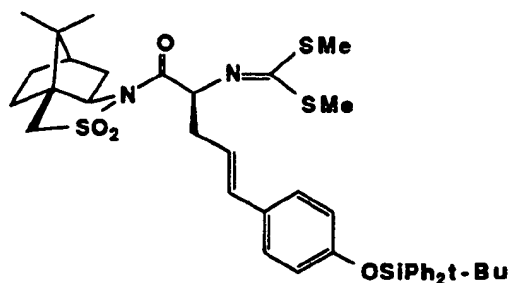
Anal. Calc. for  $\text{C}_{32}\text{H}_{49}\text{N}_4\text{O}_6 \cdot 0.34\text{H}_2\text{O}$ : C, 64.93; H, 8.46; N, 9.47. Found: C, 64.99; H, 8.20; N, 9.41.

## Example 235

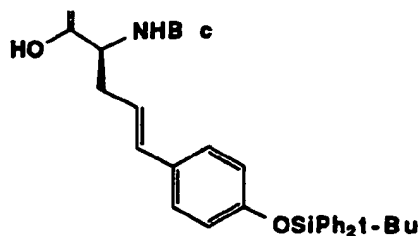
Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(E)]]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-6-(4-hydroxyphenyl)-5-hexenyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamic acid, 1,1-dimethylethyl ester (Compound 235e)

(a) Compound 235a

Compound 235a was prepared according to the procedure of Oppolzer et al., *Tetrahedron Lett.*, 30 (44), 6009 (1989).

(b) Compound 235b

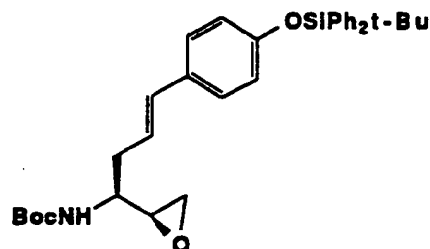
To a solution of *n*-BuLi (4.4 ml; 11.0 mmol; 2.5M in hexanes) in 25 ml of dry THF cooled at -78°C was added a solution of Compound 235a (3.77 g; 10.0 mmol) in 15 ml of dry THF. The mixture was stirred at -78°C for 1 h, followed by addition of a solution of 4-*t*-butyldiphenylsilyloxycinnamyl bromide (Young et al., *J. Med. Chem.*, 35, 1702 (1992)); 6.8 g, 15.0 mmol) in 10 ml of 1:1 THF-HMPA, dropwise over 10 min. *n*-Bu<sub>4</sub>NI (200 mg) was then added and the reaction was warmed from -78°C to RT over 2 hours. The reaction mixture was cooled back to -20°C and H<sub>2</sub>O was added. The mixture was extracted with EtOAc and the combined extracts washed with H<sub>2</sub>O and brine and dried over MgSO<sub>4</sub>. Concentration *in vacuo* gave an oily residue which was purified by flash chromatography (10:1 hexane:chloroform to 100% chloroform) on silica gel to afford 5.2 g (69%) of Compound 235b as a colorless oil which solidified upon standing.

(c) Compound 235c

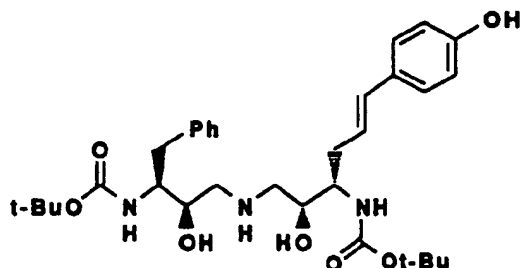
To a solution of Compound 235b (14.7 g, 19.7 mmol) in 280 ml of THF and 125 ml of DME was added a solution of 1.0 N HCl (125 ml). The homogeneous mixture was then heated at 40°C overnight. H<sub>2</sub>O (200 ml) was added and the pH was adjusted to 12 with 6N KOH. The mixture was extracted with EtOAc and the combined organic extracts washed with H<sub>2</sub>O, saturated NaHCO<sub>3</sub>, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of solvent under reduced pressure afforded 13.9 g of crude amine as an off-white foam which was used without further purification.

To the suspension of the crude amine (13.9 g) in 85 ml of dry CH<sub>3</sub>CN cooled at 0°C was added di-*t*-butyl dicarbonate (7.7 g, 32.5 mmol). The reaction mixture was stirred at RT overnight. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane-EtOAc: 4:1) on silica gel to afford 13.7 g of the N-Boc carbamate as an off-white foam.

To a solution of LiOH·H<sub>2</sub>O (1.5 g, 36.8 mmol) in H<sub>2</sub>O (36 ml) cooled at 0°C was added a solution of 30% H<sub>2</sub>O<sub>2</sub> (11.3 ml, 110 mmol). The mixture was stirred at 0°C for 1 h and added at 0°C to a solution of the above prepared N-Boc carbamate (13.7 g, 18.4 mmol) in 380 ml of 3:1 THF-H<sub>2</sub>O. The reaction mixture was stirred at 0°C for 15 min and a solution of 1.5 N Na<sub>2</sub>SO<sub>3</sub> (85 ml) was added. After stirring for another 30 min, the mixture was acidified to pH = 2 with 3N HCl and extracted with EtOAc. The combined extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration *in vacuo* followed by flash chromatography (CHCl<sub>3</sub>-MeOH-AcOH: 95:5:1) on silica gel afforded 7.74 g (77%) of Compound 235c as a white solid.

(d) Compound 235d

Compound 235c was converted to Compound 235d by a procedure analogous to that used for the preparation of Compound 175b.

(e) Compound 235e

Compounds 235d and 16b were reacted by a procedure analogous to that used for the synthesis of Compound 4b to give the title Compound 235e (off-white solid).

m.p.: 110-112 °C;  $[\alpha]_D = +1.6^\circ$  (c 0.25, MeOH).

5 Mass Spec. (FAB): 586<sup>+</sup> (M+H)<sup>+</sup>.

Anal. Calc. for C<sub>32</sub>H<sub>47</sub>N<sub>3</sub>O<sub>7</sub>·0.82 H<sub>2</sub>O: C, 64.00; H, 8.16; N, 7.00. Found: C, 64.15; H, 8.05; N, 6.85.

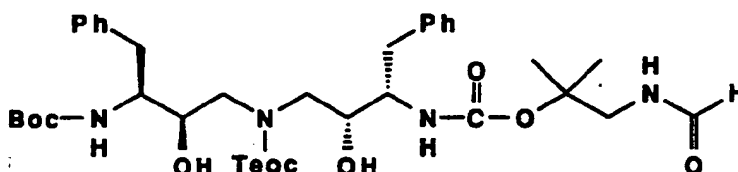
#### Example 236

10 Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2-(formylamino)-1,1-dimethylethyl 1,1-dimethylethyl ester (Compound 236b)

##### (a) Compound 236a

15

20



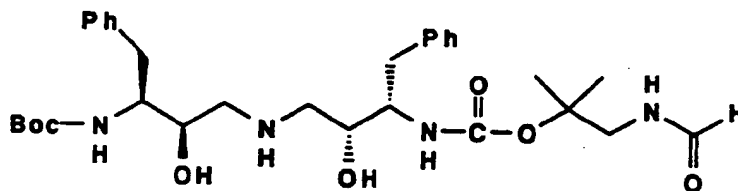
Compound 216d was reacted with formylacetic anhydride in THF by a procedure analogous to that of Example 129 to give Compound 236a.

25

##### (b) Compound 236b

30

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Compound 236a was converted to the title Compound 236b (white solid) by a procedure analogous to that of Example 21. The final product was purified by reverse phase HPLC (19 x 300 mm C18 column) eluted with a continuous gradient (30:70 A:B to 80:20 A:B; A = 90% CH<sub>3</sub>OH/H<sub>2</sub>O + 0.05% TFA; B = 10% CH<sub>3</sub>OH/H<sub>2</sub>O + 0.05% TFA). The resulting foamy white solid was lyophilized from CH<sub>3</sub>OH/H<sub>2</sub>O.

m.p. 78-81°C;  $[\alpha]_D = -7.8^\circ$  (c = 0.2, CH<sub>3</sub>OH).

45

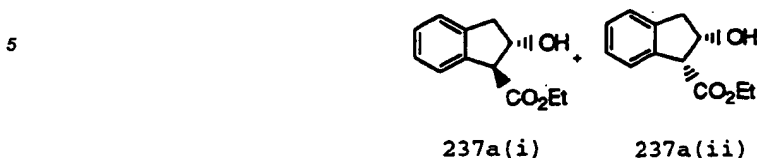
Analysis calculated for: C <sub>31</sub> H <sub>48</sub> N <sub>4</sub> O <sub>7</sub> · 1.89 H <sub>2</sub> O			
	C, 59.98;	H, 8.08;	N, 9.02.
Found:	C, 60.45;	H, 7.73;	N, 8.55.

#### Example 237

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Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(trans)]]]-[3-[[3-[(2,3-Dihydro-2-hydroxy-1H-inden-1-yl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 237c)

55

(a) Compounds 237a(i) and 237a(ii)

10

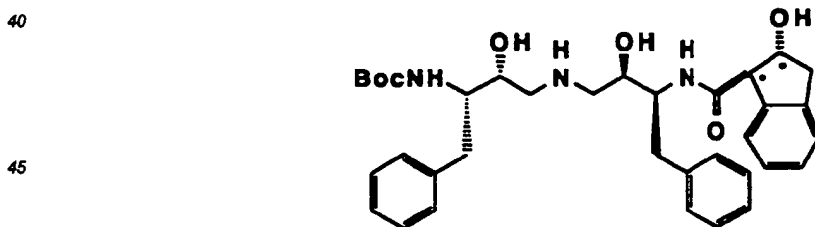
To a mixture of NaBH<sub>4</sub> (230 mg, 6.08 mmol) in aqueous EtOH (30 mL, 95%) at 0°C was added 1-carboethoxy-2-indanone (0.62 g, 3.03 mmol, prepared as in *J. Chem. Soc.*, 121, 1562-1571 (1922)). After stirring for 1 h, solid NH<sub>4</sub>Cl (140 mg, 2.61 mmol) was added and the mixture was brought to RT. More solid NH<sub>4</sub>Cl (440 mg, 8.22 mmol) was added after 2 h, followed by NaBH<sub>4</sub> (59 mg, 1.56 mmol). Further amounts of NH<sub>4</sub>Cl (995 mg over 11.5 h), and then NaBH<sub>4</sub> (573 mg over 11.5 h), were added periodically over the next 11.5 h. The mixture was evaporated *in vacuo*, the resulting residue suspended in saturated NH<sub>4</sub>Cl and extracted with EtOAc. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to an oil which was purified by flash chromatography (silica gel, 3 by 20 cm), eluting with EtOAc:CH<sub>2</sub>Cl<sub>2</sub> (1, 2, 3, and then 5% EtOAc) to give Compounds 237a(i) and 237a(ii) (350 mg, 3:2 ratio by <sup>1</sup>H NMR, 56% yield) as a colorless oil.

20

(b) Compound 237b

30 To neat Compounds 237a(i) and 237a(ii) (350 mg, 1.70 mmol) was added 1N NaOH (3 mL, 3 mmol). After 1.5 h, the solution was brought to pH 1 with 1N HCl. The resulting solution was extracted with Et<sub>2</sub>O, the combined organic layers dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give an oily solid. This residue was dissolved in hot EtOAc, diluted with hot pentane and allowed to slowly cool. After storing overnight at -20°C, the solid was triturated twice with cold pentane/EtOAc (4:1) to give after drying *in vacuo* Compound 237b (219 mg, 72% yield) as a slightly orange colored solid.

35

(c) Compound 237c

(1:1 mixture of diastereomers at •)

50

Compounds 237b and 54 were reacted by a procedure analogous to that of Example 55 (DMF only used) to give the title Compound 237c (colorless solid).  
m.p. (shrink 141°C) dec. 161-165°C; [α]<sub>D</sub> = +10.7° (c 0.41, HOAc).  
MS: (CI): 604 (M+H).

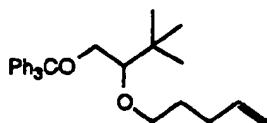
55

Anal. Calc. for $C_{36}H_{45}N_3O_6 \cdot 0.51 H_2O$			
	C, 68.58;	H, 7.57;	N, 6.86
Found:	C, 68.53;	H, 7.41;	N, 6.91

### Example 238

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[2-[3-(2-Benzimidazolyl)propoxy]-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 238e)

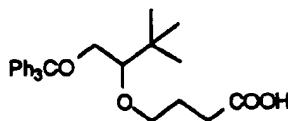
#### (a) Compound 238a



The triflate of 4-pentene-1-ol was prepared by the addition of 5.5 ml (33 mmol) of triflic anhydride in 50 ml of  $CH_2Cl_2$ , over a period of 1 hr, to a solution of 3.1 g (30 mmol) of 4-pentene-1-ol and 3.6 ml (45 mmol) of pyridine in 150 ml of  $CH_2Cl_2$ , at  $-10^\circ C$ . After the addition was complete, the cold reaction was washed twice with 1N HCl, twice with brine, sat  $NaHCO_3$ , and twice with brine. The solution was dried ( $MgSO_4$ ) and the solvent removed to yield 6.6 g (assumed 30 mmol, 100%) of the triflate as a pale yellow oil. This material was used immediately in the next step.

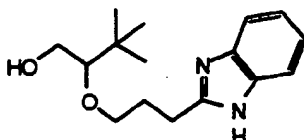
To a suspension of 1.7 g (15 mmol) of 35% KH suspension (hexane washed) in 50 ml of THF, at RT was added dropwise a solution of 4.8 g (13.3 mmoles) of Compound 106a in 25 ml of THF. After 2 h the solution was ice cooled and diluted with 75 ml of DMF. To this solution was added a solution of the freshly prepared pre-cooled ( $-78^\circ C$ ) 4-pentene-1-ol triflate in 10 ml of THF. After stirring for 0.5 h at  $0^\circ C$  and RT for 1 h, the reaction was diluted with brine and extracted twice with  $Et_2O$ . The extracts were washed with brine, dried ( $MgSO_4$ ), the solvent removed and the resulting oil purified by flash chromatography on a 400 cc column of silica gel (elution with 25%  $CH_2Cl_2$ /hexane) to afford 2.9 g (51%) of Compound 238a as a colorless oil.

#### (b) Compound 238b



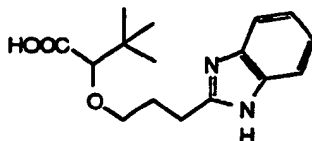
A solution of 1.7 g (4 mmoles) of Compound 238a, 1.9 g (12 mmoles) of  $KMnO_4$ , and 75 mg of  $n-Bu_4NBr$  in 20 ml of toluene, 20 ml of  $H_2O$  and 4 ml of HOAc was stirred for 2 h. To the resulting slurry was added sat.  $NaHSO_3$  with stirring until the reaction became colorless. The suspension was extracted with EtOAc and the combined extracts washed with brine, dried ( $MgSO_4$ ) and the solvent removed to yield a crude product which was purified by flash chromatography on a 125 cc column of silica gel (elution with 25% EtOAc/hexane) to afford 1.1 g (62%) of Compound 238b as a colorless oil.

#### (c) Compound 238c



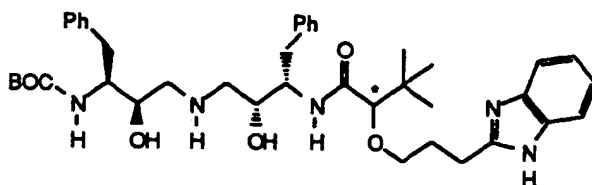
To a solution of 1.0 g (2.2 mmol) of Compound 238b and 0.42 ml (3 mmol) of Et<sub>3</sub>N in 10 ml of THF, at -10°C was added dropwise 0.32 ml (2.5 mmol) of i-butylichloroformate. After 0.5 h, a solution of 270 mg (2.5 mmol) of o-phenylenediamine in 5 ml of THF was then added. After 1.5 h at -10°C, the reaction was diluted with EtOAc and washed with H<sub>2</sub>O, sat. NaHCO<sub>3</sub>, and brine, dried (MgSO<sub>4</sub>) and the solvent removed to give 1.3 g of a white foam. This material was dissolved in 25 ml of HOAc and heated at 65°C for 3.5 hr. After cooling, the solution was evaporated to dryness. The residue was taken into EtOAc and washed with sat NaHCO<sub>3</sub> and brine. After drying (MgSO<sub>4</sub>), removal of solvent gave a residue which was purified by flash chromatography on a 125 cc column of silica gel (elution with 100% EtOAc) to give 266 mg (44%) of Compound 238c as a solid foam.

(d) Compound 238d



75 mg (0.27 mmol) of Compound 238c was converted to the corresponding aldehyde by a procedure analogous to that of Example 191c. To 50 mg of the intermediate aldehyde in 0.5 ml of THF and 0.9 ml (1.8 mmoles) of a 2M THF solution of 2-methyl-2-butene was added dropwise a solution of 23 mg (0.2 mmol) of sodium chlorite (80%) in 0.5 ml of pH 3.95 acetate buffer. After 1 h, the reaction was evaporated to dryness and the residue taken into 1 ml of H<sub>2</sub>O saturated with solid NaCl and the pH adjusted to 5.0 by the addition of HOAc. After extraction with EtOAc, the combined organic layers were washed once with minimal brine, dried (MgSO<sub>4</sub>), and the solvent removed to give a crude product which was purified by flash chromatography on a 15 cc column of silica gel (elution with 5%, 10% and 20% MeOH/CHCl<sub>3</sub>) to afford 35 mg (45%) of Compound 238d as a white solid.

(e) Compound 238e



(1:1 mixture of diastereomers at \*)

Compounds 238d and 54 were reacted by a procedure analogous to that of Example 93f to give the title Compound 238e (solid foam) as a 1:1 mixture of diastereomers.

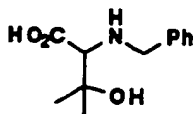
High Res Mass Spec.: (M+H)<sup>+</sup> = 716.4375; calc. 716.4387.

Calc. for C<sub>41</sub>H<sub>67</sub>N<sub>6</sub>O<sub>8</sub> · H<sub>2</sub>O (733.9): C, 67.09; H, 8.10; N, 9.54. Found: C, 67.01; H, 8.00; N, 9.21.

Example 239

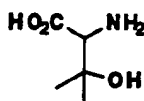
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(5,5-Dimethyl-2-oxo-4-oxazolidinyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 239d)

(a) Compound 239a



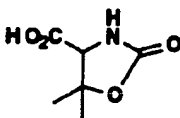
Dimethylacrylic acid and sodium tungstate were suspended in H<sub>2</sub>O (0.67 ml/g acid) the pH of which was adjusted to 6.5 with aq. NaOH. At RT, 35% aq. H<sub>2</sub>O<sub>2</sub> (4.1 mol eq.) was added dropwise maintaining the pH with additional aq. NaOH. After the addition was complete, the reaction was stirred for 1 h at 40°C at which time Na<sub>2</sub>SO<sub>3</sub> was added to destroy excess peroxide. Benzylamine was added (1.2 eq.) and the resulting mixture stirred at reflux for 2 h. The reaction was partially concentrated and then brought to pH 6 with concentrated HCl. The reaction was cooled to RT and the solid product Compound 239a filtered off and washed with cold H<sub>2</sub>O and EtOH (28%).

(b) Compound 239b



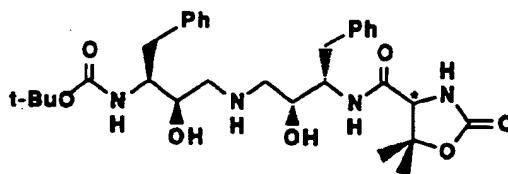
Compound 239a was stirred in MeOH (10 ml/g) along with 10% Pd/C under a H<sub>2</sub> atmosphere for 1 h (35°C). After filtering off the catalyst, the reaction was partially concentrated and then cooled to 0°C. Acetone (7 ml/g Compound 239a) was added and the resulting solid Compound 239b filtered and washed with acetone (100%).

(c) Compound 239c



To a solution of Compound 239b (1.33 g, 10.0 mmol) in 12.5% aq. KOH (37 ml) cooled at 0°C was added a solution of phosgene (1.93M) in toluene (11.7 ml). The mixture was stirred at 0°C for 1.0 h and the toluene layer was separated. The aqueous layer was washed with Et<sub>2</sub>O, acidified to pH = 3 with 3N HCl and concentrated *in vacuo* to afford a solid residue. This residue was extracted into hot methanol (200 ml) and the solid removed by filtration. The filtrate was concentrated *in vacuo* and then partitioned between 5% KHSO<sub>4</sub> and EtOAc. The aqueous layer was extracted with hot EtOAc and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 1.38 g (87%) of Compound 239c as an off-white solid.

(d) Compound 239d



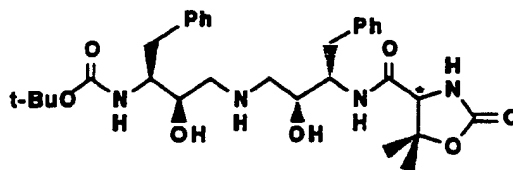
Compounds 54 and 239c were reacted by a procedure analogous to that of Example 93f to give Compound 239d along with its diastereomer Compound 240 as a 1:1 mixture. HPLC purification (S-10 C18; 120Å ODS; MeOH-H<sub>2</sub>O-TFA 60:40:0.1) gave the title Compound 239d (white solid) as the slower moving isomer. m.p. 108-110°C; [α]<sub>D</sub> -5.0° (c 0.2, MeOH). Mass Spec. (FAB): 585<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for C<sub>31</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub>:

	C, 63.68;	H, 7.58;	N, 9.51.
Found:	C, 63.75;	H, 7.79;	N, 9.51.

Example 240

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(5,5-Dimethyl-2-oxo-4-oxazolidinyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 240)



Compound 240 (white solid) was isolated by preparative HPLC (the faster moving isomer) as described in Example 239.

m.p. 120-122°C;  $[\alpha]_D = -18.3^\circ$  (c 0.25, MeOH).

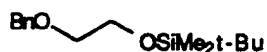
Mass Spec. (FAB): 585<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for C<sub>31</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub>·1.08H<sub>2</sub>O:

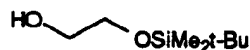
	C, 61.63;	H, 7.70;	N, 9.27.
Found:	C, 61.70;	H, 7.62;	N, 9.20.

Example 241

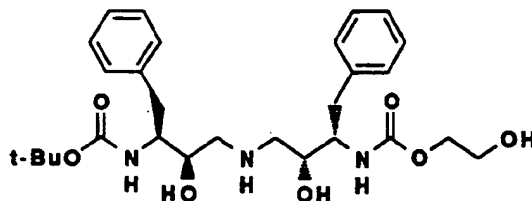
Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-2-hydroxyethyl ester (Compound 241c)

(a) Compound 241a

Benzyloxyethanol was converted to Compound 241a by a procedure analogous to that of Example 161c.

(b) Compound 241b

Compound 241a was converted to Compound 241b by a procedure analogous to that of Example 7.

(c) Compound 241c



Compounds 241b and 48 were converted to the title Compound 241c (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used as the solvent in the coupling reaction of Compound 48 with the p-nitrophenyl carbonate of Compound 241b).

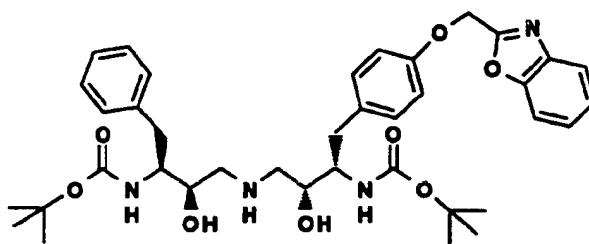
m.p. = 168°-172°C;  $[\alpha]_D = -8.3^\circ$  (c = 0.32; MeOH)

MS (FAB): (M + H)<sup>+</sup> = 532;

Elemental Analysis: (for C <sub>28</sub> H <sub>41</sub> N <sub>3</sub> O <sub>7</sub> ·0.27 H <sub>2</sub> O)			
Calculated:	C, 62.68;	H, 7.80;	N, 7.83
Found:	C, 62.69;	H, 7.68;	N, 7.82.

#### Example 242

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[4-[(2-Benzoxazolyl)methoxy]phenyl]-3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxybutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 242)



Compounds 171a and 172 were reacted by a four-step procedure analogous to that used for the conversion of Compound 172 to Compound 178 to give the title Compound 242 (white solid).

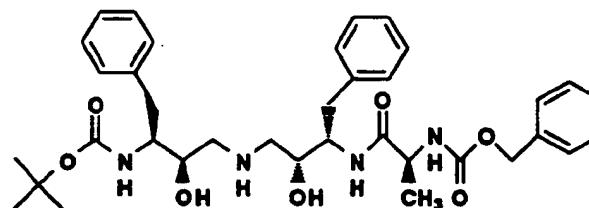
mp 145-150°C;  $[\alpha]_{365} = -21.7^\circ$  (c 0.27, MeOH).

Mass Spec. FAB + ions: M+H = 691

Analysis calc. for C <sub>38</sub> H <sub>50</sub> N <sub>4</sub> O <sub>8</sub> ·1.09 H <sub>2</sub> O:			
	C, 64.24;	H, 7.40;	N, 7.89;
Found:	C, 64.16;	H, 7.14;	N, 7.97.

#### Example 243

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-alanamide (Compound 243)



Compound 54 and N-carbobenzyloxy-L-alanine were reacted by a procedure analogous to that of Example 55 (DMF only used) to give the title Compound 243 (white solid).

mp 156-157°C,  $[\alpha]_D = -10^\circ$  (c 0.10, MeOH).

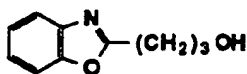
Mass Spec. IONSpray + ions: (M + H)<sup>+</sup> = 649.

Analysis calc. for $C_{36}H_{48}N_4O_7 \cdot 0.25H_2O$ :			
	C, 66.18;	H, 7.48;	N, 8.58;
Found:	C, 66.21;	H, 7.47;	N, 8.55.

### Example 244

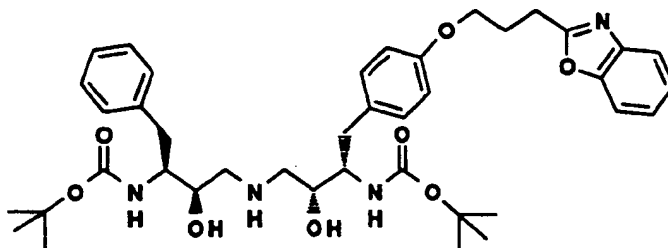
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[3-[(2-benzoxazolyl)propoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl-ethyl ester (Compound 244b)

#### (a) Compound 244a



A mixture of o-aminophenol (2.5 g; 23 mmol), 4-pentenoic acid (2.33 ml; 23 mmol) and p-toluenesulfonic acid (150 mg) in 50 ml of toluene was refluxed with azeotropic removal of  $H_2O$  for 30 hours. After cooling to RT, the reaction mixture was partitioned between EtOAc and 1N NaOH and the organic layer washed with 1N NaOH,  $H_2O$  and brine. After drying over  $MgSO_4$  and decolorizing over charcoal (Darco), the organic layer was filtered and concentrated to afford 793 mg (20%) of the intermediate, benzoxazole-2-prop-3-ene, as a yellow liquid. Ozone was bubbled through a solution of this intermediate (492 mg; 2.8 mmol) in 13 ml of MeOH at  $-78^\circ$  for ~3 min. The reaction was stopped when starting material was consumed by TLC (EtOAc:Hex, 1:1). After purging with oxygen, the reaction mixture was warmed to  $-35^\circ C$  and 1.5 ml of  $H_2O$ , followed by  $NaBH_4$  (163 mg; 4.2 mmol), was added. The reaction mixture was warmed to  $0^\circ C$  over 1 h, at which time saturated aqueous  $NH_4Cl$  (3 ml) was added. Most of the MeOH was removed *in vacuo* and the residue was partitioned between EtOAc and saturated aqueous  $NH_4Cl$ . The organic layer was washed with saturated aqueous  $NH_4Cl$  and brine. After drying over  $MgSO_4$  and concentrating, the residue was chromatographed on a 2.5 x 5 cm silica gel column using EtOAc as the mobile phase to afford 400 mg (81%) of Compound 244a as an orange solid.

#### (b) Compound 244b



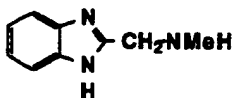
Compounds 244a and 172 were reacted by a four-step procedure analogous to that used for the conversion of Compound 172 to Compound 178 to give the title Compound 244b (white solid). mp  $121-126^\circ C$ ;  $[\alpha]_{365} = -3.6^\circ$  (c 0.48, MeOH).

Mass Spec. FAB + ions:  $M+H = 719$

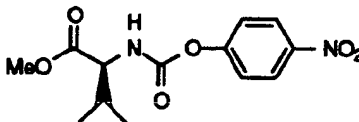
Analysis calc. for $C_{40}H_{64}N_4O_8 \cdot 1.28 H_2O$ :			
	C, 64.75;	H, 7.68;	N, 7.55;
Found:	C, 64.59;	H, 7.43;	N, 7.71.

**Example 245**

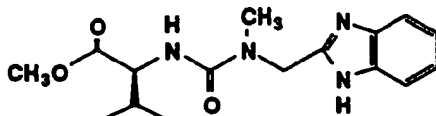
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[[[(1H-benzimidazol-2-ylmethyl)methylamino]carbonyl]-L-valinamide (Compound 245d)

**(a) Compound 245a**

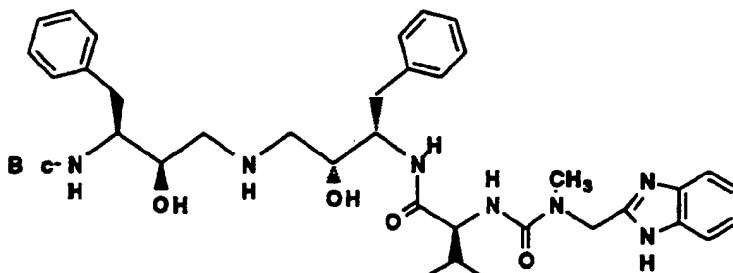
To a 40% aqueous solution of methylamine (100 ml) cooled to 0°C was slowly added 2-chloromethyl benzimidazole (6.0 g, 36 mmol). After 1 additional h at 0°C the reaction was diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated *in vacuo* to give a crude product which was purified on a silica column eluting with a gradient from 5 to 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.1 % NH<sub>4</sub>OH to afford 680 mg (12%) Compound 245a as a colorless solid.

**(b) Compound 245b**

Pyridine (1.19 g; 15 mmol) was added to a suspension of L-valine methyl ester hydrochloride (1 g; 6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0°C. p-Nitrophenylchloroformate (1.33 g; 6.6 mmol) was added and the mixture stirred at 0°C for 2 h and at RT for 1 h. The reaction was diluted with EtOAc and washed with 10% KHSO<sub>4</sub>, sat. NaHCO<sub>3</sub>, H<sub>2</sub>O and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 1.4 g (80%) of Compound 245b as a pale-yellow solid.

**(c) Compound 245c**

A mixture of Compound 245a (282 mg, 1.75 mmol), Compound 245b (518 mg, 1.75 mmol), and Et<sub>3</sub>N (354 mg, 3.5 mmol) in 9 ml of dry CH<sub>3</sub>CN was stirred overnight at RT. The volatiles were evaporated to give a crude product which was purified on a silica column eluting with a gradient from 2 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.1% NH<sub>4</sub>OH to afford 136 mg (24%) of Compound 245c as a colorless solid.

**(d) Compound 245d**

Compounds 245c and 54 were reacted by a two-step procedure analogous to that used for the conversion of Compound 70b to Compound 70d (DMF only; no N-methyl morpholine was added) to give the title Compound 245d (colorless solid).

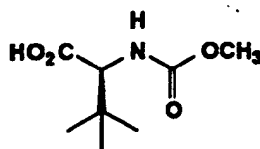
m.p. 184–188°C (dec);  $[\alpha]_D^{25} = -18.5^\circ$  ( $c = 0.25$ , MeOH)

High Res. Mass Spec. (FAB): (M+H)<sup>+</sup> = 730.4292<sup>+</sup>; C<sub>40</sub>H<sub>58</sub>N<sub>7</sub>O<sub>8</sub> Δ = 1.5 ppm.

### Example 246

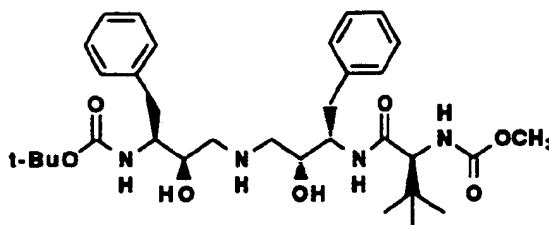
**Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(phenylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide (Compound 246b)**

**(a) Compound 246a**



To a 0°C solution of (L)-t-leucine (0.600 g, 4.57 mmol) in aqueous NaOH (2.80 mL of a 2.0 N solution) were added in alternate portions methyl chloroformate (0.388 mL, 5.03 mmol) and aqueous NaOH (2.20 mL of a 2.0 N solution) over 5 min. The solution was stirred at 0°C for 30 min and for 1 h at RT. The aqueous solution was washed with Et<sub>2</sub>O, acidified with aqueous 3 M HCl solution to pH 1 and extracted with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the Compound 246a (0.867 g, ≅100%) as a colorless glass, which was used in the next step without purification.

**(b) Compound 246b**



To a 0°C solution of Compound 246a (0.094 g, 0.496 mmol) and HOBT.H<sub>2</sub>O (0.114 g, 0.744 mmol) in DMF (1.0 mL) was added EDC (0.095 g, 0.496 mmol). The solution was stirred at 0°C for 1 h. Compound 54 (200 mg, 0.451 mmol) in 1 ml DMF was added followed by N-methyl morpholine (0.165 mL, 1.50 mmol). The solution was allowed to warm to RT and stir for 36 h at which time volatiles were removed *in vacuo*. The residue was partitioned between aqueous 50% NaHCO<sub>3</sub> and EtOAc. The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to give solid, which was chromatographed on silica gel (100 mL) using a gradient from 99:1:0.1 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH as eluent to afford Compound 246b as a white solid (135 mg; 49%).

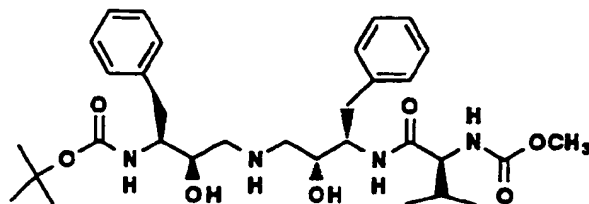
m.p. = 153°-156°C;  $[\alpha]_D^{25} = -16.1^\circ$  (c = 0.33; MeOH)

MS (FAB):  $(M + H)^+ = 615$ ;

Elemental Analysis: (for C <sub>33</sub> H <sub>50</sub> N <sub>4</sub> O <sub>7</sub> · 1.09 H <sub>2</sub> O)			
Calculated:	C, 62.48;	H, 8.29;	N, 8.83
Found:	C, 62.48;	H, 8.06;	N, 8.83.

**Exempl 247**

Preparation of [1R\*, 2S\*, 3R\*]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(methoxycarbonyl)-L-valinamide (Compound 247)



Compound 54 and L-valine were converted into the title Compound 247 (white solid) by a two-step procedure analogous to that of Example 246.

m.p. 202-205°C;  $[\alpha]_D = -33.3^\circ$  (c 0.06, MeOH)

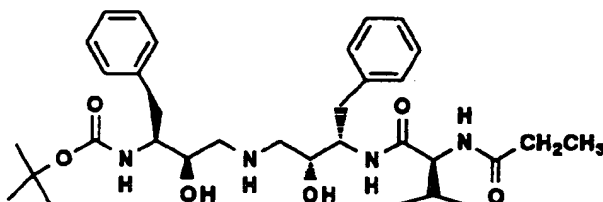
Analysis Calc. for  $C_{32}H_{48}O_7N_4 \cdot 0.28 H_2O$

C, 63.44; H, 8.08; N, 9.25

Found: C, 63.51; H, 8.03; N, 9.18.

**Example 248**

Preparation of [1R\*, 2S\*, (2S\*, 3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(1-oxopropyl)-L-valinamide (Compound 248)



Compound 61 and propionic acid were converted into the title Compound 248 (white solid) by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52.

m.p. 222-225°C;  $[\alpha]_D = -28.5^\circ$  (c 0.07, MeOH)

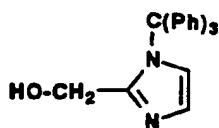
Analysis Calc. for  $C_{32}H_{50}O_6N_4 \cdot 0.64 H_2O$ :

	C, 64.95;	H, 8.47;	N, 9.18
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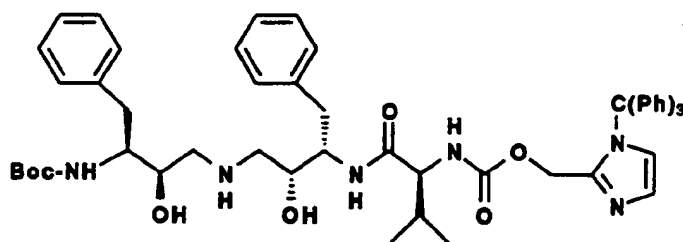
Found:	C, 64.90;	H, 8.31;	N, 9.23.
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**Example 249**

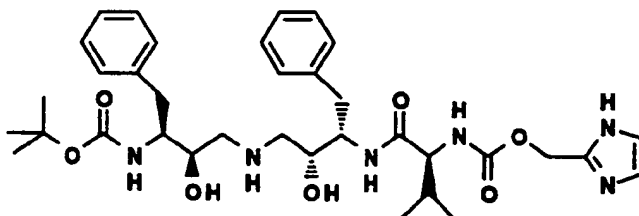
Preparation of [1R\*, 2S\*, (2S\*, 3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(1H-imidazol-2-ylmethoxy)carbonyl]-L-valinamide, acetate (2:3) salt (Compound 249c)

(a) Compound 249a

To a solution containing 1-trityl-2-formyl imidazole (1.54 g, 4.55 mmol; *J. Org. Chem.*, 43, 4381 (1978)) in a mixture of 12 mL of THF and 12 mL of EtOH cooled to 0°C was added portionwise NaBH<sub>4</sub> (300 mg, 7.93 mmol). After 45 min at 0°C, the cold reaction mixture was quenched with pH 4 phosphate buffer and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford 1.47 g of Compound 249a as a waxy solid (95%, crude yield).

(b) Compound 249b

Compound 249a and 61 were converted into Compound 249b by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (Et<sub>3</sub>N was used in the coupling of Compound 61 with the *p*-nitrophenyl carbonate of Compound 249a).

(c) Compound 249c

Compound 249b (250 mg, 0.275 mmol) was dissolved in a mixture of 3 mL of absolute EtOH and 12 mL of HOAc. The reaction mixture was heated at 40°C for 3.5 h in a stoppered flask, then concentrated *in vacuo* and triturated with CH<sub>2</sub>Cl<sub>2</sub>-hexanes to afford the title Compound 249c (180 mg, 83%) as a white solid. m.p. (softens 129°C), 135-152°C; [α]<sub>D</sub> = +1.2° (c = 0.21, MeOH).

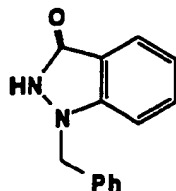
MS (FAB): (M+H)<sup>+</sup> = 667<sup>+</sup>

Elemental Analysis: Calcd for C<sub>35</sub>H<sub>50</sub>N<sub>8</sub>O<sub>7</sub> · 1.5 C<sub>2</sub>H<sub>4</sub>O<sub>2</sub> · 1.8 H<sub>2</sub>O: C, 57.82; H, 7.61; N, 10.65.

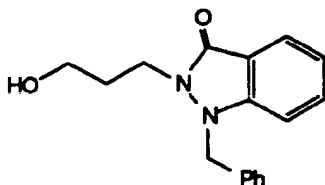
Found: C, 57.77; H, 7.27; N, 11.04.

Example 250

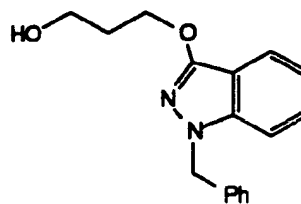
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[3-(1,3-Dihydro-3-oxo-2H-indazol-2-yl)-1-oxopropyl]-N-[3-[[[1,1-dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamid (Compound 250)

(a) Compound 250a

To a solution of 0.380 mg (16.5 mmol) of Na metal in 25 mL of anhydrous EtOH was added 2.01 g (15.0 mmol) of indazolinone. The resulting suspension was heated at reflux for 15 min at which point 1.9 mL (16.5 mmol) of benzyl chloride was added over 15 min. The resulting mixture was heated at reflux for 7 h, cooled to RT, concentrated *in vacuo*, and the residue diluted with 150 mL of 1N NaOH. The mixture was extracted with Et<sub>2</sub>O. The aqueous layer was acidified to pH=5 with HOAc and then extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* and the solid recrystallized from H<sub>2</sub>O/MeOH to give 990 mg (29%) of Compound 250a.

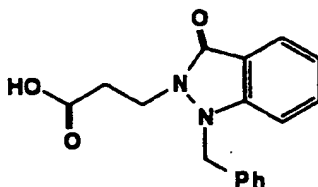
(b) Compound 250b(i)

250b(i)



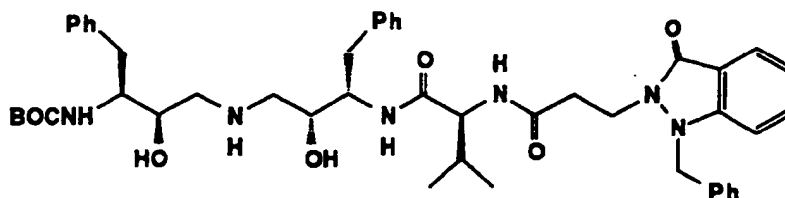
250b(ii)

To a solution of 0.253 mg (11.0 mmol) of Na metal in 20 mL of anhydrous EtOH was added 2.29 g (10.2 mmol) of Compound 250a. The mixture was heated at reflux for 15 min at which point 1.13 mL (12.0 mmol) of 3-bromopropanol in 5 mL of toluene was added over 10 min. After 4 h, an additional 0.38 mL (1.1 mmol; 21% wt in ethanol) of sodium ethoxide and 0.1 mL of 3-bromopropanol were added. The mixture was heated at reflux for 2 h, and then stirred at RT for 12 h. The cooled mixture was concentrated *in vacuo*, and the residue was diluted with 150 mL of 1N NaOH. The mixture was extracted with Et<sub>2</sub>O and the extracts washed with brine dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (10-50% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>; then, 5% CH<sub>3</sub>OH-CH<sub>2</sub>Cl<sub>2</sub>) provided 634 mg (22%) of Compound 250a(i) [TLC Rf=0.10 (10% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>)] and 2 g of Compound 250b(ii) [TLC Rf=0.37 (10% EtOAc-CH<sub>2</sub>Cl<sub>2</sub>)].

(c) Compound 250c

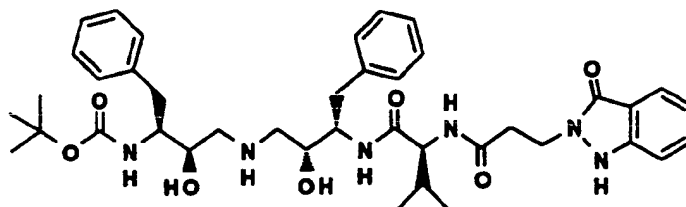
To a solution of 200 mg (0.708 mmol) of Compound 250b(i) in 3.5 mL of dry DMF was added 1.03 g (2.73 mmol) of pyridinium dichromate. The mixture was stirred at RT for 18 h then poured into 1:1 H<sub>2</sub>O/brine (100 mL) and extracted with Et<sub>2</sub>O. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and evaporated *in vacuo* to give 130 mg (62%) of Compound 250c.

## (d) Compound 250d



To a solution of 238 mg (0.439 mmol) of Compound 59, 130 mg (0.439 mmol) of Compound 250c, and 119 mg (0.88 mmol) of HOBT in 2.5 mL of dry DMF at 0°C was added 93 mg (0.483 mmol) of EDCI. The mixture was stirred at 0°C for 3 h and at RT for 18 h then concentrated *in vacuo*. The residue was diluted with EtOAc, and washed with saturated NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine. The organic layer was concentrated *in vacuo*, and purified by flash chromatography on silica gel [2-10% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> with 1.0% NH<sub>4</sub>OH] to provide 265 mg [74% yield (88% pure by HPLC)] of Compound 250d.

## (e) Compound 250e



A solution of 185 mg (0.225 mmol) of Compound 250d in 12 mL of hot MeOH was cooled to RT, and treated with 100 mg of 10% Pd/C. The mixture was stirred under a H<sub>2</sub> atmosphere for 24 h then an additional 100 mg of 10% Pd/C was added and the mixture was stirred under a H<sub>2</sub> atmosphere for another 12 h. The mixture was filtered, rinsed with hot MeOH, and evaporated *in vacuo*. Flash chromatography of the residue on silica gel [2% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>, then 3-10% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> (with 0.3-1.0% NH<sub>4</sub>OH)] provided 81 mg (49%) of the title Compound 250e (colorless solid).

mp 187-192°C (dec.); [ $\alpha$ ]<sub>D</sub> = -22° (c 0.32, CH<sub>3</sub>OH)

Mass Spec: 731 (M+H)<sup>+</sup>

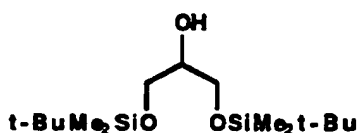
Elemental Analysis: Calcd for C<sub>40</sub>H<sub>64</sub>N<sub>6</sub>O<sub>7</sub> · 0.32 H<sub>2</sub>O:

	C, 65.21;	H, 7.48;	N, 11.41.
Found:	C, 65.31;	H, 7.53;	N, 11.31.

## Example 251

Preparation of [R-(R\*,S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-bis(hydroxymethyl)ethyl 1,1-dimethylethyl ester (Compound 251d)

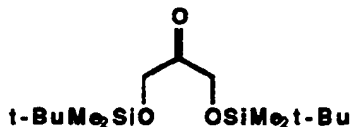
## (a) Compound 251a





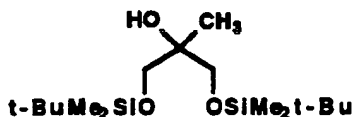
Compound 251a was prepared by the method described in Curran et al., *Synthetic Comm.* 20, 3575 (1990).

5 (b) Compound 251b



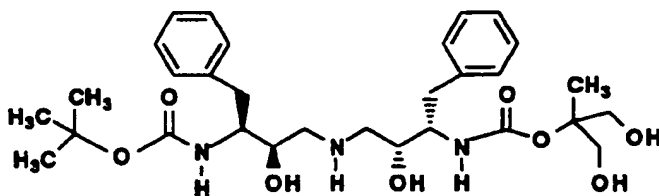
10 To a slurry of (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) (3.8 g, 8.96 mmol) in 10 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added *t*-BuOH (0.929 mL, 9.856 mmol). The mixture was cooled to 0°C and a solution of Compound 251a (1.434 g, 4.48 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added. The reaction mixture was warmed to RT and stirred for 2 h after which time the mixture was diluted with 75 mL of EtOAc and 90 mL of 1:1:1 sat. NaHCO<sub>3</sub>-10% Na<sub>2</sub>SO<sub>3</sub>-brine was added. The mixture was stirred vigorously for 1 h, the two phases separated and the organic phase washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The crude residue was purified by flash chromatography on silica, eluting with a stepwise gradient of hexane to 50% EtOAc-hexane to obtain Compound 251b (0.775 g, 54%) as a colorless oil.

(c) Compound 251c



25 To 1.95 mL (2.681 mmol) of a 1.4M MeLi solution in Et<sub>2</sub>O was added 5 mL of THF. The solution was cooled to -78°C and a solution of Compound 251b (0.775 g, 2.437 mmol) in 5 mL of THF was slowly added. An additional 1 mL of MeLi solution was added twice at intervals of 1 h and the mixture slowly warmed to -40°C. After 1 additional h, the reaction was quenched by adding 0.4 mL of HOAc in 5 mL of THF, warmed to RT and diluted with H<sub>2</sub>O. The mixture was extracted with EtOAc and the extracts washed with sat. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and concentrated. The crude residue was purified by flash chromatography on silica gel eluting with a stepwise gradient of hexane to 75% EtOAc-hexane to afford Compound 251c (0.475 g, 58%) as a colorless oil.

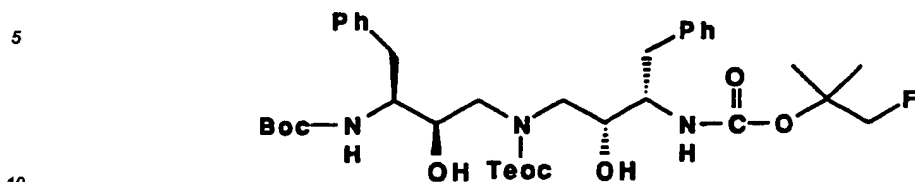
40 (d) Compound 251d



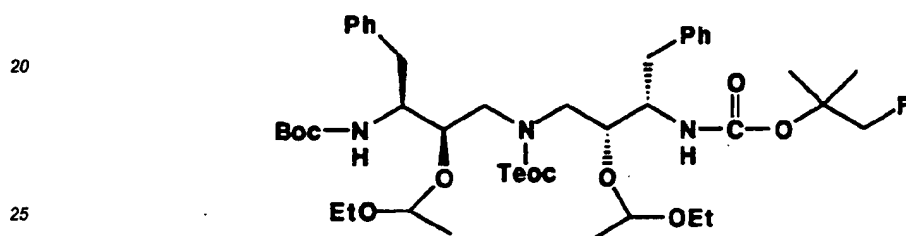
50 Compounds 161a and 251c were reacted by a five-step procedure analogous to that used for the conversion of Compound 161c to Compound 162 (Et<sub>3</sub>N was used in the coupling of the *p*-nitrophenyl carbonate of Compound 251c with Compound 161a) to give the title Compound 251d (off-white solid). High Res. Mass Spec. (M+H)<sup>+</sup> = 576.3285 (Δ<sub>ppm</sub> = 2.2).

55 Example 252

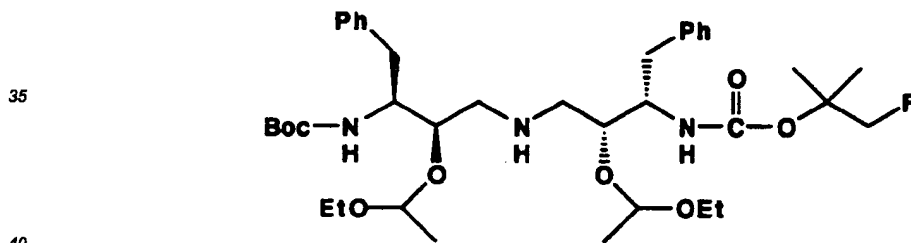
Preparation f [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 2-fluoro-1,1-dimethylethyl 1,1-dimethylethyl ester (Compound 252d)

(a) Compound 252a

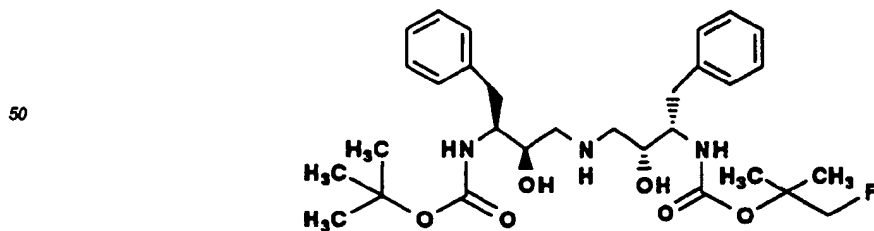
Compound 48 and 2-methyl-1-fluoro-2-propanol (Bergmann et al., *J. Chem. Soc.*, 2259 (1958)) were converted to Compound 252a by a two-step procedure analogous to that used for the conversion of Compound 149c to 149e.

(b) Compound 252b

Compound 252a was converted to Compound 252b by a procedure analogous to that of Example 140a.

(c) Compound 252c

Compound 252b was converted to Compound 252c by a procedure analogous to that of Example 21.

(d) Compound 252d

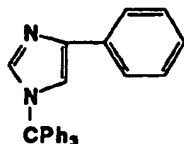
Compound 252c was converted to the title Compound 252d (white solid) by a procedure analogous to that of Example 140 except that the reaction was run at RT for 18 h and at reflux for 2 h. m.p. 174-176°C;  $[\alpha]_D = -6.0^\circ$  (c = 0.2, CH<sub>3</sub>OH)

Analysis calculated for:  $C_{30}H_{44}N_3O_6F$ 

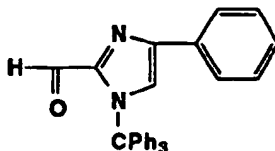
	C, 64.15;	H, 7.90;	N, 7.48;	F, 3.38.
Found:	C, 63.99;	H, 7.96;	N, 7.81;	F, 3.35.

**Example 253**

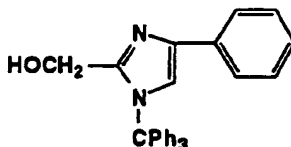
**Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl(4-phenyl-1H-imidazol-2-yl)methyl ester (Compound 253e)**

**(a) Compound 253a**

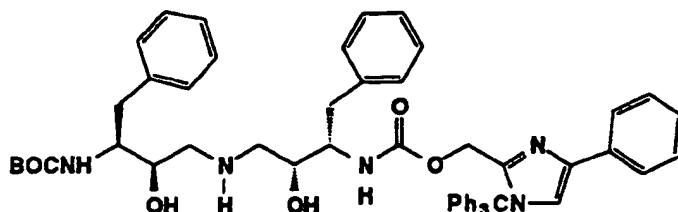
4-phenylimidazole (2.5 g, 17.3 mmol) was stirred with trityl chloride (4.8 g, 17.2 mmol) in acetone (37 ml) and  $Et_3N$  (2.9 ml, 20.8 mmol) for 3 h. The mixture was concentrated, dissolved in  $CH_2Cl_2$  and washed with  $H_2O$ , brine, dried ( $Na_2SO_4$ ) and concentrated. The product crystallized and was dried *in vacuo* to yield Compound 253a (6.49 g, 97%, mp 185-188°C).

**(b) Compound 253b**

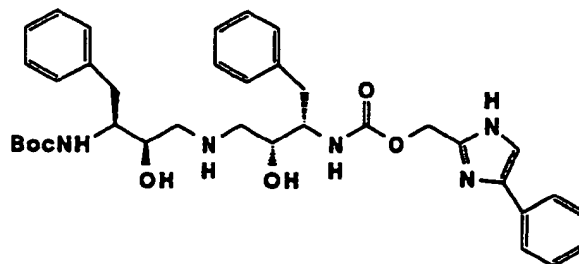
Compound 253a (2.0 g, 5.17 mmol) in 50 ml of dry THF was cooled to -45°C and tert-butyl lithium (1.7M in hexanes, 6.1 ml, 10.34 mmol) was added dropwise and the reaction was stirred for 30 min. DMF (1.9 ml, 25.85 mmol) was added and the reaction was stirred for 1.5 h at which point saturated aq.  $NH_4Cl$  was added and product was extracted with EtOAc. The EtOAc solution was washed with  $H_2O$ , brine, dried ( $Na_2SO_4$ ), and concentrated *in vacuo* to yield crystalline Compound 253b (2.09 g, 94%, mp 185-188°C).

**(c) Compound 253c**

Compound 253b (2.09 g, 5.0 mmol) was dissolved in THF:EtOH: $CHCl_3$  (15 ml:15 ml:20 ml), cooled to 0°C and  $NaBH_4$  (0.33 g, 8.57 mmol) was added portionwise. After 1 h, the reaction mixture was diluted with  $CH_2Cl_2$  and washed with  $H_2O$ , brine, dried ( $Na_2SO_4$ ) and concentrated. The product crystallized from  $Et_2O$  to yield Compound 253c (1.8 g, 86%, mp 183-190°C).

(d) Compound 253d

Compounds 253c and 48 were reacted by a three-step procedure analogous to that used for the conversion of Compound 149c to 150 (Et<sub>3</sub>N and DMF were used in the reaction of the p-nitrophenyl carbonate of Compound 253c with Compound 48) to give Compound 253d.

(e) Compound 253e

Compound 253d was dissolved in EtOH (4.7 mL) and HOAc (19 mL) and the reaction mixture was stirred at 40°C for 2 h, concentrated *in vacuo* and the residue triturated with Et<sub>2</sub>O. The resulting solid was chromatographed through 80 g of silica gel eluting with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (89:10:1) to afford the title Compound 253e (0.12 g, 54%) as a white solid.

m.p. 109-115°C; [α]<sub>D</sub> = -5.6° (c = 0.85, MeOH).

Analysis Calc. for C<sub>38</sub>H<sub>45</sub>N<sub>5</sub>O<sub>8</sub>·1.13 H<sub>2</sub>O:

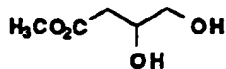
	C, 65.11;	H, 7.17;	N, 10.55
Found:	C, 65.12;	H, 6.99;	N, 10.54

Example 254

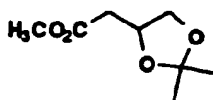
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(3,4-dihydroxy-1-oxobutyl)-L-valinamide (Compound 254f)

(a) Compound 254a

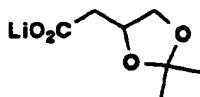
To a 0°C solution of diazomethane/Et<sub>2</sub>O (see Compound 1a(i) for preparation) was added dropwise 3-butenic acid (4.94 mL, 58.0 mmol) over 5 min. The solution was swirled until colorless, then washed with aqueous NaHCO<sub>3</sub> and dried (Na<sub>2</sub>SO<sub>4</sub>). The Et<sub>2</sub>O was distilled off to give Compound 254a (4.32 g, 74%).

(b) Compound 254b

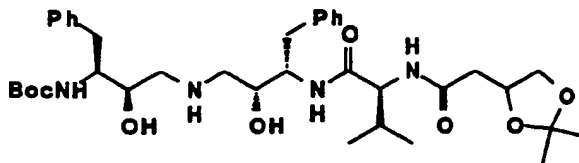
To a solution of Compound 254a (4.25 g, 42.4 mmol) and N-methylmorpholine N-oxide (8.07 mL of a 60% solution by weight in H<sub>2</sub>O) in acetone (30 mL) and H<sub>2</sub>O (20 mL) was added OSO<sub>4</sub> (70.0 mg, 0.275 mmol) and the resulting solution stirred at RT for 18 h. A solution of NaHSO<sub>3</sub> (0.50 g in 5 mL H<sub>2</sub>O) was then added, the resulting black solution stirred at RT for 30 min, then filtered through Celite (acetone wash). The volatiles were removed and the residual aqueous solution was saturated with NaCl and extracted with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and purified on silica gel (150 mL) using a gradient from 1:1 hexane:EtOAc to 100% EtOAc to give Compound 254b (3.15 g, 55%) as a slightly yellow oil.

(c) Compound 254c

To a solution of Compound 254b (1.00 g, 7.46 mmol) in acetone (10 mL) and 2,2-dimethoxypropane (10 mL) was added p-toluenesulfonic acid hydrate (7 mg, 0.037 mmol) and the solution was stirred at RT for 18 h. Saturated aqueous NaHCO<sub>3</sub> solution was added and the mixture was concentrated *in vacuo*. The residue was partitioned between H<sub>2</sub>O and EtOAc and the combined organic extracts were washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The oil was purified on silica gel (150 mL) using 10:1 hexane:EtOAc to give Compound 254c (1.260 g, 97%) as a colorless oil.

(d) Compound 254d

Compound 254c was converted to Compound 254d by a procedure analogous to that of Example 70c (THF used as solvent).

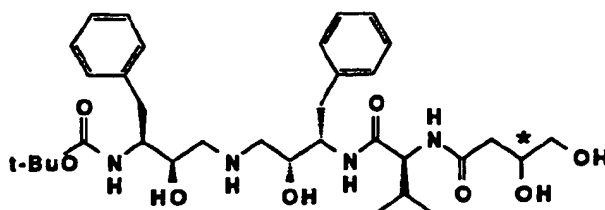
(e) Compound 254e

Compounds 254d and 61 were reacted by a two step procedure analogous to that used for the conversion of Compound 48 to Compound 52 to give Compound 254e (white foam).

(f) Compound 254f

5

10



(1:1 mixture at \*)

15 Compound 254e was converted to the title Compound 254f (white solid; mixture of diastereomers at \*) by a procedure analogous to that of Example 202c.

m.p. = 156°-160°C;  $[\alpha]_D = -11.1^\circ$  (c = 0.28; MeOH) High resolution Mass Spec. (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>34</sub>H<sub>53</sub>N<sub>4</sub>O<sub>8</sub>) = 645.3861;

Observed (M + H)<sup>+</sup> = 645.3862 Δ = 0.2 ppm

20

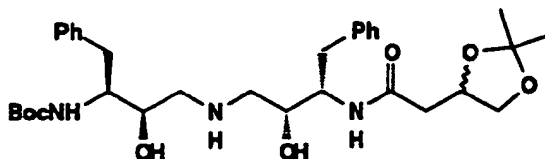
Example 255

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-(3,4-Dihydroxy-1-oxo-butyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 255b)

25

(a) Compound 255a

30



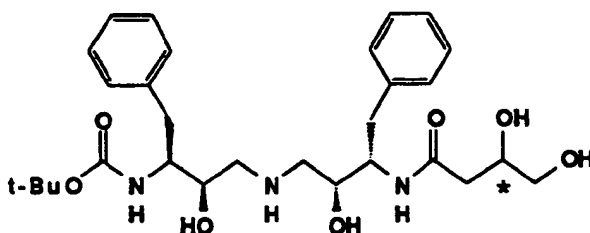
35

Compounds 254d and 48 were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to 52 to give Compound 255a (white solid).

(b) Compound 255b

40

45



(1:1 mixture of diastereomers at \*)

50

Compound 255a was converted to the title Compound 255b (white solid; mixture of diastereomers) by a procedure analogous to that of Example 202c.

m.p. = 145°-150°C;  $[\alpha]_D = +5.0^\circ$  (c = 0.20; MeOH)

Mass Spec. (FAB): (M + H)<sup>+</sup> = 546;

55

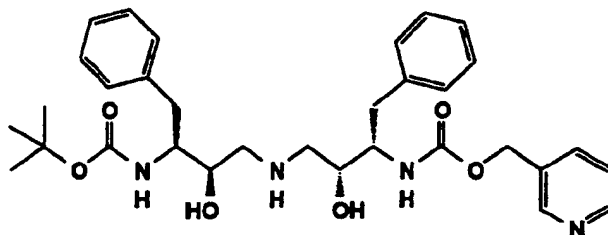
Elemental Analysis: (for C<sub>28</sub>H<sub>43</sub>N<sub>3</sub>O<sub>7</sub> · 1.19 H<sub>2</sub>O)

Calculated: C, 61.42; H, 8.07; N, 7.41

Found: C, 61.20; H, 7.83; N, 7.63

## Exempl 256

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-3-pyridinylmethyl ester (Compound 256)



3-Pyridine carbinol and Compound 48 were converted to the title Compound 256 (colorless solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate of 3-pyridine carbinol to Compound 48).

m.p. 167-170°C;  $[\alpha]_D = -16^\circ$  (c 0.24, CH<sub>3</sub>OH)

Mass Spec. 579 (M+H)<sup>+</sup>

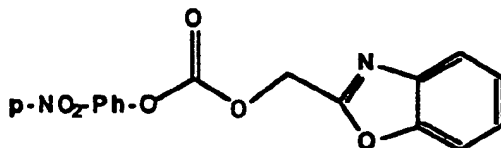
Analysis Calc. for C<sub>32</sub>H<sub>42</sub>N<sub>4</sub>O<sub>8</sub>·0.37 H<sub>2</sub>O:

	C, 65.66;	H, 7.36;	N, 9.57
Found:	C, 65.65;	H, 7.39;	N, 9.58

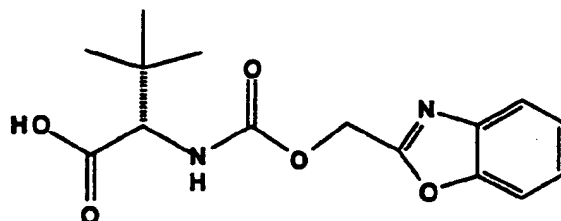
## Example 257

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-benzoxazolyl)methyl ester (Compound 257c)

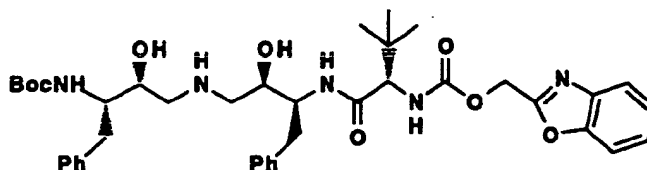
## (a) Compound 257a



To a solution of 350 mg (2.35 mmol) of Compound 171a in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and 2.5 mL of pyridine at 0°C was added 475 mg (2.35 mmol) of p-nitrophenylchloroformate in 2.5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred at 0°C for 2 h. The mixture was diluted with EtOAc and washed with 1M NaOH, H<sub>2</sub>O, and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*. Flash chromatography of the residue (20-40% EtOAc-hexane) afforded 567 mg (77%) of Compound 257a.

(b) Compound 257b

To neat tert-L-leucine (146 mg, 1.11 mmol) was added aqueous 1 N NaOH (1.1 mL). After stirring for several minutes, a dioxane (3 mL) solution of Compound 257a (140 mg, 2.61 mmol) was added, followed by Et<sub>3</sub>N (0.23 mL, 1.65 mmol). The reaction mixture was stirred for 26 h, diluted with H<sub>2</sub>O, and brought to pH 4 with 5% KHSO<sub>4</sub>. The aqueous solution was extracted with EtOAc, the aqueous layer brought back to pH 3 with more 5% KHSO<sub>4</sub> and extracted with EtOAc. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to an oil. The residue was purified by flash chromatography (silica gel, 3 by 15 cm), eluting with EtOAc:CH<sub>2</sub>Cl<sub>2</sub> (1:1), then 10% MeOH:CH<sub>2</sub>Cl<sub>2</sub> to give Compound 257b (227.7 mg, 67% yield) as a colorless oily solid.

(c) Compound 257c

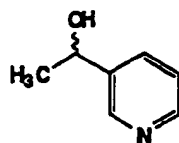
To a solution of Compound 257b (152 mg, 0.50 mmol) in DMF (2.5 mL) at 0°C under argon was added HOBT (105 mg, 0.78 mmol), and then EDCI (95 mg, 0.50 mmol). After 45 min, solid Compound 54 (226 mg, 0.51 mmol) was added and the mixture was brought to RT. After stirring 24 h, the reaction mixture was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to give an oily solid which was purified by flash chromatography (silica gel, 3 by 15 cm), eluting with MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub> (5:0.5:94.5, 6:0.6:93.4, and then 7:0.7:92.3) to give the title Compound 257c (151 mg, 42% yield) as a colorless solid. m.p. 149-159°C; [α]<sub>D</sub><sup>25</sup> = -18.2° (c 0.28, MeOH). Mass Spec.: (FAB): 732 (M+H).

Anal. Calc. for C <sub>40</sub> H <sub>53</sub> N <sub>5</sub> O <sub>8</sub>			
	C, 65.64;	H, 7.30;	N, 9.57
Found:	C, 65.79;	H, 7.54;	N, 9.66

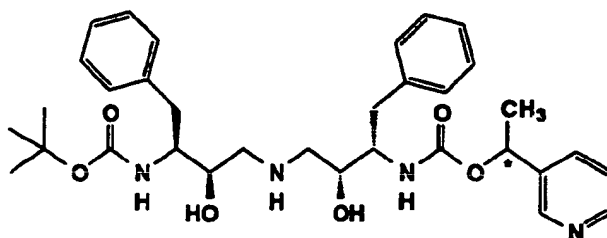
Example 258

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-1-(3-pyridinyl)ethyl ester (Compound 258b)



(a) Compound 258a

To a solution of 536 mg (5.00 mmol) of 3-pyridinecarboxaldehyde in 16.5 mL of dry THF at -78°C was added 3.4 mL (5.5 mmol) of methyllithium (1.6M in Et<sub>2</sub>O) (internal temperature < -55°C). The resulting yellow solution was warmed to 0°C and quenched by the addition of 30 mL of saturated NH<sub>4</sub>Cl. The reaction mixture was extracted with Et<sub>2</sub>O and the organic layer dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to provide 458 mg of Compound 258a. The aqueous layer was saturated with NaCl and extracted with Et<sub>2</sub>O. Concentration *in vacuo* provided an additional 74 mg (total 532 mg) of product.

(b) Compound 258b

(1:1 mixture of stereoisomers at \*)

Compounds 258a and 48 were converted to the title Compound 258b (colorless solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate of Compound 258a to Compound 48).

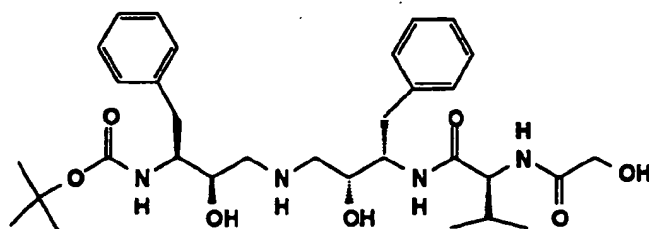
m.p. 161-170°C;  $[\alpha]_D^{25} = -14^\circ$  (c 0.21, CH<sub>3</sub>OH)

Mass Spec. 593 (M+H)<sup>+</sup>

Anal. Calc. for C <sub>33</sub> H <sub>44</sub> N <sub>4</sub> O <sub>8</sub>			
	C, 66.87;	H, 7.48;	N, 9.45
Found:	C, 66.54;	H, 7.64;	N, 9.28

Example 259

Preparation of [1R\*, 2S\* (2S\*, 3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(hydroxyacetyl)-L-valinamide (Compound 259)



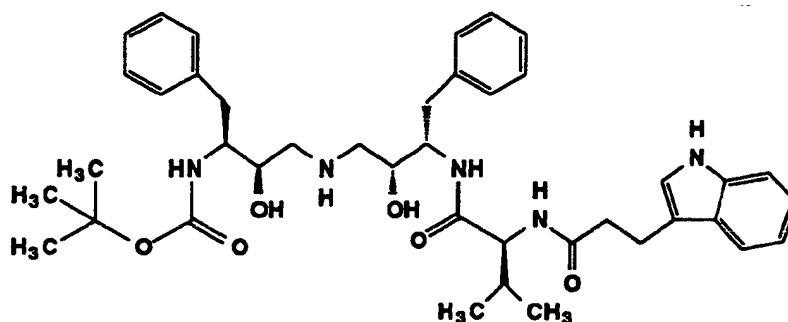
Compound 61 and glycolic acid were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52 to afford the title Compound 259 (white solid).  
m.p. 208-210°C

5 Mass Spec. High resolution 601.3595, error 1.0 ppm, theory 601.3601

Analysis Calc. for $C_{32}H_{48}O_7N_4 \cdot 1.34 H_2O$ :			
	C, 61.50;	H, 8.17;	N, 8.97
Found:	C, 61.77;	H, 8.15;	N, 8.70

#### Example 260

15 Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[3-(1H-indol-3-yl)-1-oxo-propyl]-L-valinamide (Compound 260)



Compound 61 and 3-indolpropionic acid were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to Compound 52 to afford the title Compound 260 (white solid). m.p. 212-214°C;  $[\alpha]_D = -38.1^\circ$  (c = 0.2, CH<sub>3</sub>OH)

Analysis for:  $C_{41}H_{55}N_5O_8 \cdot 0.65 H_2O$

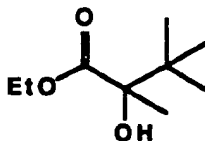
35 Calculated: C, 67.86; H, 7.82; N, 9.65.

Found: C, 67.95; H, 7.77; N, 9.56.

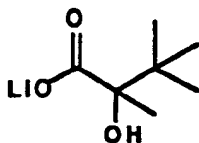
#### Example 261

40 Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(R\*)]]]-[3-[[3-[(2-Hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 261c)

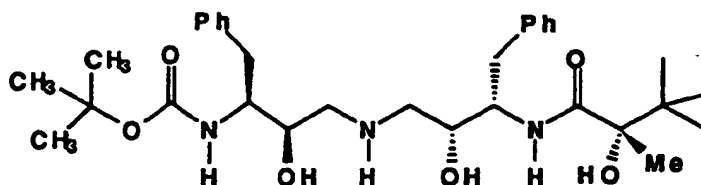
45 (a) Compound 261a



55 A solution of t-butyl magnesium chloride (2 M in Et<sub>2</sub>O, 21.55 mL, 43.1 mmol) was added to a stirred solution of ethyl pyruvate (5 g, 43.1 mmol) in THF (75 mL) at -78°C. The reaction mixture was stirred at -78°C for 15 min, RT for 1 h, diluted with EtOAc, and washed with 1N HCl followed by sat. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>), concentrated, and the resulting oil was fractionally distilled under vacuum affording 3.5 g (47%) of Compound 261a as a colorless oil (b.p. 45-50°C at 1.2 mm).

(b) Compound 261b

A 0.5 M aq. solution of LiOH (10.64 mL) was added to a solution of Compound 261a (1.0 g, 5.75 mmol), stirred at 75°C for 8 h, concentrated *in vacuo*, and the residue concentrated from toluene. The residue was triturated from Et<sub>2</sub>O to afford 0.9 g (ca. 100%) of Compound 261b.

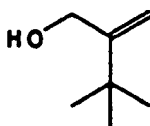
(c) Compound 261c

To a solution of Compound 261b (0.114 g, 0.75 mmol), HOBT monohydrate (0.135 g, 0.88 mmol) in 2 mL dry DMF at 0°C was added N-methyl morpholine (0.1634 mL, 1.49 mmol), EDCI hydrochloride (0.1434 g, 0.75 mmol) and the resulting mixture was stirred at 0°C for 15 min. The mixture was treated with Compound 54 (0.3 g, 0.68 mmol) and stirred at RT for 20 h, concentrated, and the residue partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried (MgSO<sub>4</sub>), concentrated, and the crude product was subjected to flash chromatography (silica gel/CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH 95:5:0.5) affording 0.193 mg (50%) of a mixture of the two diastereomeric products. This mixture was subjected to prep. HPLC (Waters Prep Nova-Pack HR C18, 6 micron, 30X300 mm; eluent: MeOH-water-TFA 30:70:0.05 to 90:10:0.05; UV 254 nm). The fractions from the slower moving isomer were made basic with sat. NaHCO<sub>3</sub>, concentrated, and the residue partitioned between EtOAc/1:1 brine-sat. NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), concentrated, the resulting white solid was triturated from 10:1 hexane-Et<sub>2</sub>O to afford 19 mg (5%) of the title Compound 261c as a white solid. m.p. 97-100°C; [α]<sub>D</sub> = -5.2° (c = 0.91, MeOH).

High resolution Mass Spec.: (M+H)<sup>+</sup> = 572.3688, theoretical: (M+H)<sup>+</sup> = 572.3699 (Δ 1.9 ppm error). Similar work-up of the fractions from the faster moving peak afforded 23 mg (6%) of Compound 262f.

## Example 262

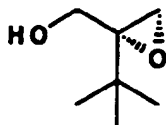
Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(S\*)]]]-[3-[[3-[(2-Hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 262f)

(a) Compound 262a

A 70% solution of t-butyl hydroperoxide in water (340.5 mL, 2.38 mol) was extracted with 300 mL CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was added to a stirred mixture of SeO<sub>2</sub> (3.67 g, 33.1 mmol) and benzoic acid (8.1 g, 66.2 mmol) in 50 mL CH<sub>2</sub>Cl<sub>2</sub>. The mixture was cooled to 0°C and 2,3,3-trimethylbutene (65 g, 0.662 mol) was added and the mixture stirred at RT for 14 h. The mixture was washed with 5% aq. KOH, brine and dried (MgSO<sub>4</sub>). The volatiles were removed by distillation and the residue was cooled to ca. 0°C. 100 mL HOAc was added followed by 100 mL M 2S added dropwise over 15 min. The reaction was stirred at RT for 3 h, cooled to 0°C

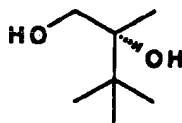
and made basic with 20% aq.  $K_2CO_3$ . The mixture was extracted with  $Et_2O$  and the organic extracts washed with sat.  $NaHCO_3$ , dried ( $MgSO_4$ ), and the solvent removed by distillation at atmospheric pressure followed by distillation of the product (90-100°C, 25 mm) to afford 20 g (26.5%) of Compound 262a.

(b) Compound 262b



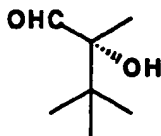
Diethyl D-tartrate (618 mg, 3 mmol) and  $Ti(iPrO)_4$  (0.744 ml, 2.5 mmol) were added to a stirred suspension of 4Å activated powdered molecular sieves in 175 ml dry  $CH_2Cl_2$  at 0°C. The mixture was cooled to -20°C and a 5.5 M solution of t-butyl hydroperoxide in 2,2,4-trimethylpentane (18.2 ml, 100 mmol) was added. After 20 min, a solution of Compound 262a (5.7 g, 50 mmol) in 25 ml  $CH_2Cl_2$  was added and the mixture stirred at -20°C for 14 h. After warming to 0°C, 15 ml  $H_2O$  was added, the mixture stirred at RT for 30 min, 30% aq. NaOH saturated with NaCl (3 ml) was added and the reaction stirred at RT for 25 min. The aqueous layer was extracted with  $CH_2Cl_2$ , the combined extracts dried ( $MgSO_4$ ) and concentrated by distillation at atmospheric pressure followed by distillation of Compound 262b (105-107°C, 25 mm; 4.75 g, 73%).

(c) Compound 262c



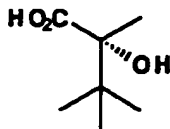
A solution of Compound 262b (2.3 g, 17.7 mmol) in 10 ml  $Et_2O$  was added to a suspension of  $LiAlH_4$  (1.477 g, 38.9 mmol) in 100 ml  $Et_2O$  at -5°C and stirred at RT for 30 min. The mixture was cooled to 0°C, and quenched with 10% aq.  $H_2SO_4$  saturated with  $Na_2SO_4$ . The aqueous layer was extracted with  $EtOAc$  and the combined extracts washed with sat.  $NaHCO_3$  and brine and dried ( $MgSO_4$ ). Concentration *in vacuo* followed by recrystallization from hexane gave 1.5 g (64%) of Compound 262c as a white solid.

(d) Compound 262d



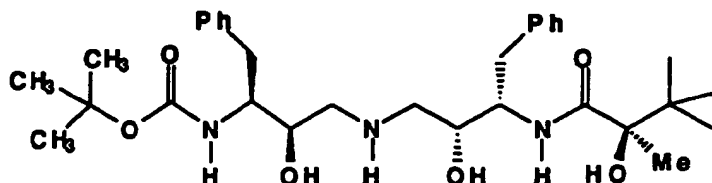
A solution of DMSO (2.578 ml, 36.3 mmol) in 3 ml  $CH_2Cl_2$  was added dropwise at -78°C to a stirred solution of oxalyl chloride (1.585 ml, 18.2 mmol) over 5 min. and stirred at -78°C for 10 min. A solution of Compound 262c (2.18 g, 16.5 mmol) in 25 ml  $CH_2Cl_2$  was added dropwise and stirred for 15 min. at -78°C.  $Et_3N$  (11.51 ml, 82.6 mmol) was added and the reaction allowed to come to RT. The mixture was diluted with additional  $CH_2Cl_2$ , washed with 10%  $H_2SO_4$ , the combined aqueous phase extracted with  $CH_2Cl_2$ , and the combined organic layer washed with sat.  $NaHCO_3$ , dried ( $MgSO_4$ ), and concentrated by distillation at atmospheric pressure to afford 2.15 g (100%) of Compound 262d as a pale gummy solid.

(e) Compound 262e



NaClO<sub>2</sub> (1.81 g, 20 mmol) and sulfamic acid (1.94 g, 20 mmol) were added in succession to a stirred solution of Compound 262d (2.0 g, 15.4 mmol) in 30 ml 1:1 THF-water at 0°C. The mixture was allowed to warm to RT, stirred for 30 min., diluted with CH<sub>2</sub>Cl<sub>2</sub> and ca. 1 ml Me<sub>2</sub>S was added followed by a small quantity of H<sub>2</sub>O. The organic layer was separated, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic layer was dried (MgSO<sub>4</sub>) and concentrated to afford a yellow gummy solid which was recrystallized from hexanes to afford 1.45 g (64.5%) of Compound 262e as a pale solid.

(f) Compound 262f



N-methylmorpholine (0.037 ml, 0.34 mmol) and BOP-reagent (150 mg, 0.34 mmol) were added at RT in succession to a stirred mixture of Compound 262e (45 mg, 0.31 mmol) and Compound 54 (137 mg, 0.31 mmol) in 0.5 ml dry DMF. The mixture was stirred at RT for 60 h, concentrated *in vacuo*, the residue partitioned between EtOAc and sat. NaHCO<sub>3</sub>, and the organic layer dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by flash chromatography (1" X12" silica gel/CH<sub>2</sub>Cl<sub>2</sub> to CH<sub>2</sub>Cl<sub>2</sub>:MeOH:aq.NH<sub>4</sub>OH 99:1:0.1 stepwise to 92.5:7.5:0.75) to afford 120 mg (68%) of the title Compound 262f as a white solid. m.p. 204 - 205°C.

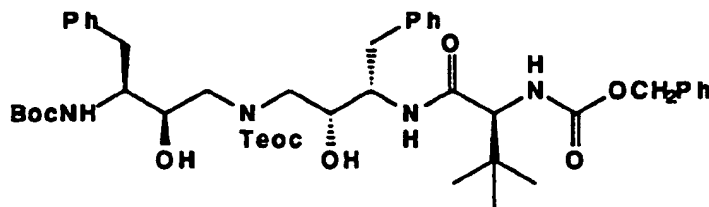
Anal. Calcd. for C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>8</sub> · 1.22 H<sub>2</sub>O:

	C, 64.73;	H, 8.73;	N, 7.08
Found:	C, 64.73;	H, 8.42;	N, 7.10.

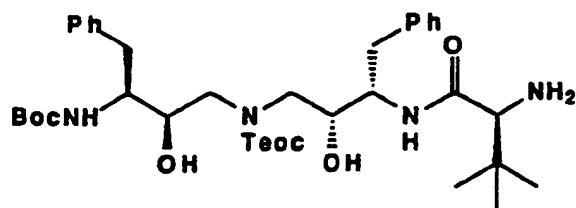
Example 263

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N'-[[[(methylamino)carbonyl]-3-methyl-L-valinamide] (Compound 263d)

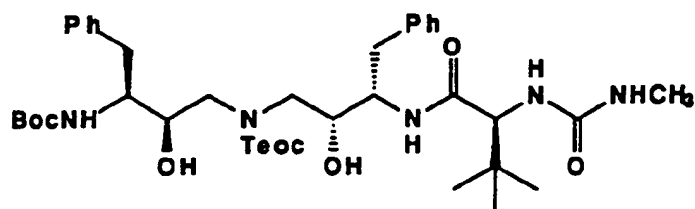
(a) Compound 263a



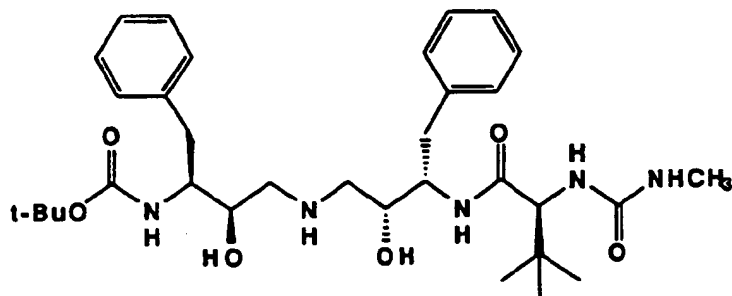
Compounds 88a and 48 were reacted by a procedure analogous to that of Example 51 to give Compound 263a (white foam).

(b) Compound 263b

Compound 263a was converted to Compound 263b (white foam) by a procedure analogous to that of Example 61.

(c) Compound 263c

Compound 263b and methyl isocyanate were reacted by a procedure analogous to that of Example 46 to give Compound 263c (colorless oil).

(d) Compound 263d

Compound 263c was converted to the title Compound 263d (white solid) by a procedure analogous to that of Example 21.

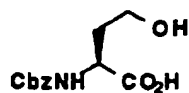
m.p. = 174°-178°C ;  $[\alpha]_D = 15.0^\circ$  (c = 0.28; MeOH)

High resolution Mass Spec. (FAB): Calculated (M + H)<sup>+</sup> (for C<sub>33</sub>H<sub>52</sub>O<sub>8</sub>N<sub>6</sub>) = 614.3917;

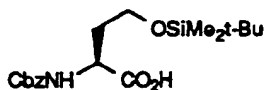
Observed (M + H)<sup>+</sup> = 614.3936  $\Delta$  = 3.1 ppm.

50 Example 264

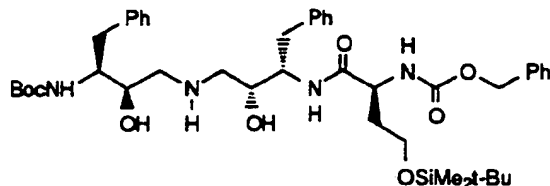
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(phenylmethoxy)carbonyl]-L-homoserinamide (Compound 264d)

(a) Compound 264a

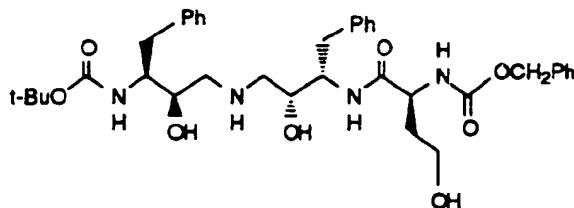
To a solution of L-homo-serine (596 mg, 5.0 mmol) and  $\text{NaHCO}_3$  (420 mg, 5.0 mmol) in 14 ml of  $\text{H}_2\text{O}$ -acetone (1:1) was added N-benzyloxycarbonyloxy succinimide (1.25 g, 5.0 mmol). The mixture was stirred overnight at RT. Acetone was removed under reduced pressure. The aqueous solution was washed with  $\text{CH}_2\text{Cl}_2$  and then acidified to pH 2.5 with 6N HCl solution and extracted with EtOAc. The combined extracts were washed with  $\text{H}_2\text{O}$  and brine and dried ( $\text{Na}_2\text{SO}_4$ ). Concentration *in vacuo* afforded 980 mg (77%) of Compound 264a.

(b) Compound 264b

To a stirred solution of Compound 264a (506 mg, 2.0 mmol) in 10 ml of dry DMF was added *tert*-butyldimethylsilyl chloride (1.81 g, 12.0 mmol), followed by imidazole (1.63 g, 24.0 mmol). The mixture was stirred for 24 h at RT.  $\text{CH}_3\text{OH}$  (35 ml) was added and the mixture was stirred for another 14 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with 10% citric acid and brine and dried over  $\text{Na}_2\text{SO}_4$ . Concentration *in vacuo* followed by flash chromatography ( $\text{CHCl}_3$ -EtOAc-HOAc: 60:40:1) afforded 638 mg (87%) of Compound 264b as a colorless oil.

(c) Compound 264c

Compounds 54 and 264b were reacted by a procedure analogous to that of Example 93f to give Compound 264c.

(d) Compound 264d

Compound 264c was converted to the title Compound 264d (white solid) by a procedure analogous to that of Example 162.

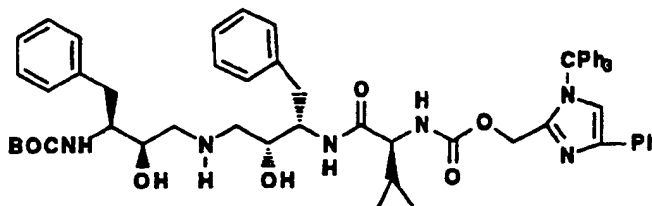
m.p. 168-170°C;  $[\alpha]_D = -25.6^\circ$  (c 0.36, M OH).  
Mass Spec. (FAB): 679<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for  $C_{37}H_{60}N_4O_8 \cdot 0.20H_2O$ :

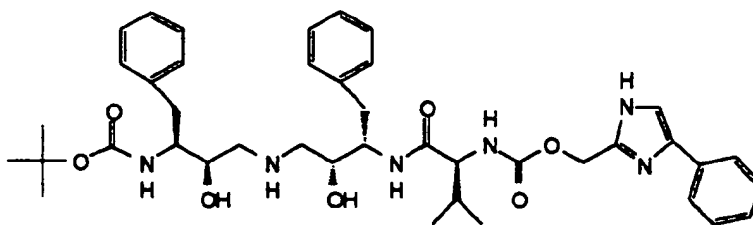
	C, 65.12;	H, 7.44;	N, 8.21.
Found:	C, 65.04;	H, 7.48;	N, 8.29.

**Example 265**

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N²-[[[4-phenyl-1H-imidazol-2-yl)methoxy]carbonyl]-L-valinamide (Compound 265b)

**(a) Compound 265a**

Compounds 253c and 61 were reacted by a three-step procedure analogous to that used for the conversion of Compound 149c to 150 ( $Et_3N$  and DMF were used in the reaction of the p-nitrophenyl carbonate of Compound 253c with Compound 61) to give Compound 265a.

**(b) Compound 265b**

Compound 265a was converted to Compound 265b (white solid) by a procedure analogous to that of Example 253e.

m.p. 140-145°C;  $[\alpha]_D = -1.8^\circ$  (MeOH, c = 0.5)

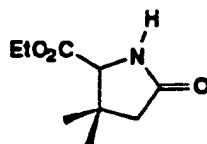
Analysis Calc. for  $C_{41}H_{54}N_6O_7 \cdot 1.61H_2O$ :

	C, 63.80;	H, 7.47;	N, 10.89.
Found:	C, 63.75;	H, 7.39;	N, 10.94.

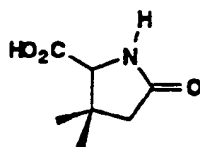
**Example 266**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(3,3-Dimethyl-5-oxo-2-pyrrolidinyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl ethyl ester (Compound 266c)

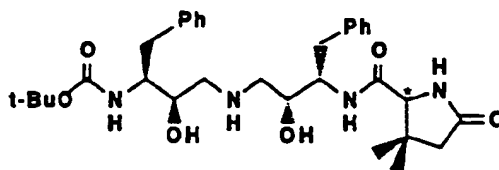


(a) Compound 266a

Compound 266a was prepared by the method of Yamazaki et al., *Chem. Pharm. Bull.*, 24, 3011 (1976).

(b) Compound 266b

Compound 266a was converted to Compound 266b by a procedure analogous to that of Example 70c (except THF:H<sub>2</sub>O:DME (2:1:0.5) was used).

(c) Compound 266c

(single isomer at \*)

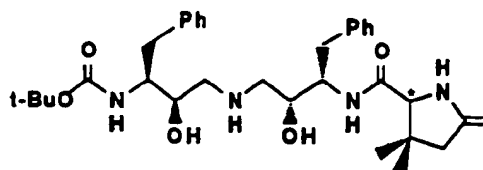
Compounds 266b and 54 were reacted by a procedure analogous to that of Example 93f to give the title Compound 266c along with its diastereomer Compound 267 (1:1). Compound 266c (white lyophilate) was isolated by flash chromatography (CHCl<sub>3</sub>-MeOH-NH<sub>4</sub>OH 95:5:0.5 to 90:10:1) on silica gel followed by preparative HPLC (CH<sub>3</sub>CN-H<sub>2</sub>O-TFA 62:38:0.1) purification (YMC SH ODS-365-10, S-10 column).

<sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ 7.10-7.30 (m, 10H), 4.27 (m, 1H), 3.70 (s, 1H), 3.58-3.75 (m, 3H), 3.14 (m, 2H), 2.50-2.84 (m, 6H), 2.26 (d, J = 16.7, 1H), 1.93 (d, J = 16.7, 1H), 1.29 (s, 9H), 0.79 (s, 3H), 0.76 (s, 3H).

High resolution Mass Spec. Calc. for C<sub>32</sub>H<sub>47</sub>N<sub>4</sub>O<sub>6</sub>: 583.3496; Found: 583.3506, Δ = 1.7 ppm.

Example 267

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(3,3-Dimethyl-5-oxo-2-pyrrolidinyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 267)



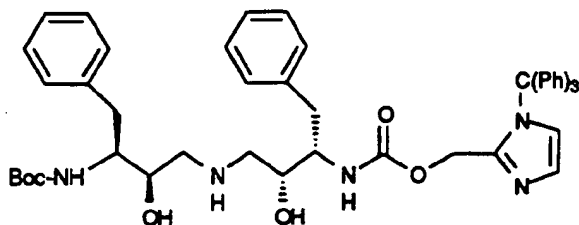
(single isomer at \*)

Compound 267, the diastereomer of Compound 266c, was isolated by preparative HPLC as described in  
Exempl 266c.  
<sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ 7.10-7.30 (m, 10H), 4.16 (m, 1H), 3.63 (s, 1H), 3.56-3.73 (m, 3H), 3.10 (m, 2H),  
 2.63-2.80 (m, 5H), 2.58 (m, 1H), 2.47 (d, J = 16.7, 1H), 2.38 (d, J = 16.7, 1H), 1.29 (s, 9H), 0.97 (s, 3H), 0.93  
 (s, 3H).  
 High resolution Mass Spec. Calc. for C<sub>27</sub>H<sub>47</sub>N<sub>4</sub>O<sub>8</sub>: 583.3496; Found: 583.3505, Δ = 1.7 ppm.

### Example 268

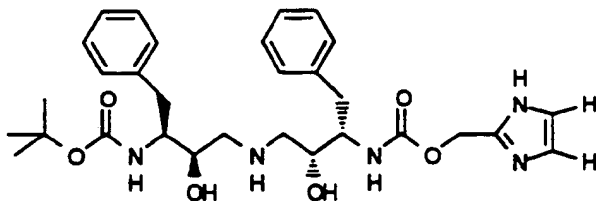
**Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, (1H-imidazol-2-yl)-methyl 1,1-dimethylethyl ester (Compound 268b)**

**(a) Compound 268a**



Compounds 249a and 48 were reacted by a three-step procedure analogous to that used for the conversion of Compound 149c to 150 (Et<sub>3</sub>N and DMF were used in the reaction of the p-nitrophenyl carbonate of Compound 249a with Compound 48) to give Compound 268a.

**(b) Compound 268b**



Compound 268a was converted to Compound 268b (white solid) by a procedure analogous to that of Example 253e.

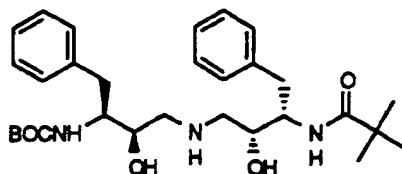
m.p. 143-147°C (dec.);  $[\alpha]_D = -5.9^\circ$  ( $c = 0.16$ , MeOH).

Analysis Calcd. for $C_{30}H_{41}N_5O_8 \cdot 0.45 H_2O$ (575.79):			
	C, 62.58;	H, 7.34;	N, 12.16.
Found:	C, 62.57;	H, 7.35;	N, 12.08.

**Mass Spec. (FAB):** (M+H)<sup>+</sup> = 568<sup>+</sup>

### Example 269

Preparation of [1S-[1R,2S\*(2S\*,3R\*)]]-3-[[3-[(2,2-Dimethyl-1-oxo-propyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl ester (Compound 269)



Compound 54 and trimethylacetic acid were converted to the title Compound 269 (white solid) by a procedure analogous to that of Example 262f except that a mixture of DMF and  $\text{CH}_2\text{Cl}_2$  was used and no N-methylmorpholine was added.

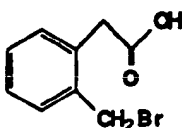
m.p. 100-104°C ("softening" at 84-99°C);  $[\alpha]_D^{20} = +10.1^\circ$  ( $c=0.8.5$ , MeOH).

High resolution Mass Spec. 528.3428\* for  $\text{C}_{30}\text{H}_{48}\text{O}_5\text{N}_3$  (calc. 528.3437\*)  $\Delta = 1.7\text{ppm}$ .

#### Example 270

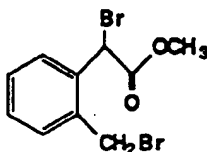
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2-Formyl-2,3-dihydro-1H-isoindol-1-yl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 270g)

#### (a) Compound 270a



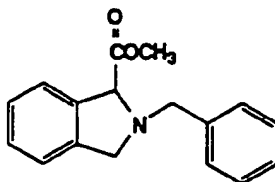
A solution of benzoyl peroxide (97%; 0.043 g), N-bromosuccinimide (11.74 g, 0.066 mol) and o-tolylacetic acid (10.0 g, 0.066 mol) in  $\text{CCl}_4$  (600 ml) was heated at 90°C for 3.5 h. Upon cooling, the reaction was filtered to remove a yellow precipitate, and the filtrate was concentrated *in vacuo* to a yellow solid. This solid was recrystallized from  $\text{CCl}_4$  to afford 9.20 g (64%) of Compound 270a as a white crystalline solid.

#### (b) Compound 270b



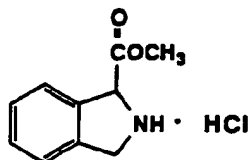
After heating a solution of Compound 270a (9.0 g, 0.04 mol) in  $\text{SOCl}_2$  (9.0 ml) at 50°C for 3 h, the excess reagent was removed at reduced pressure, and the resulting yellow oil heated to 80°C under a 250 watt lamp.  $\text{Br}_2$  (2.5 ml) was added and the reaction continued at 80°C for 4 h before cooling and removing the excess reagent under reduced pressure. The resulting brown residue was stirred in MeOH for 30 min at RT then concentrated *in vacuo* to an orange oil which was chromatographed on a silica gel column, eluting the column with toluene to afford 8.0 g (65%) of Compound 270b as a yellow oil.

#### (c) Compound 270c



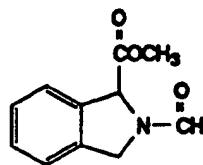
Benzylamin (2.04 ml, 18.69 mmol) was added to a stirred solution of Compound 270b (2.0 g, 6.23 mmol) in toluene (13 ml) at 0°C. The reaction was warmed to RT where it remained for 72 h before filtering off a yellow precipitate under Ar. The solid was washed thoroughly with toluene and the filtrate diluted with a solution of anhydrous Et<sub>2</sub>O saturated with HCl gas. The mother liquor was decanted and the remaining yellow gum dried under high vacuum to afford 1.35 g (50%) of Compound 270c as a green foam.

(d) Compound 270d



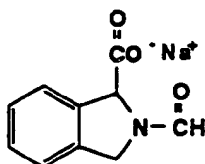
Compound 270c was converted to Compound 270d by a procedure analogous to that of Example 2.

(e) Compound 270e



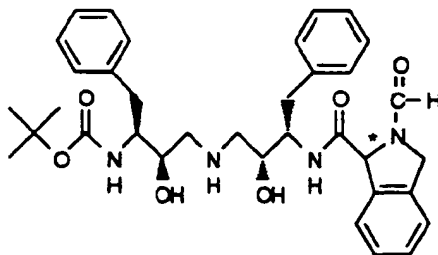
Compound 270d was converted to Compound 270e by a procedure analogous to that of Example 129 (except 1.1 eq. of N-methylmorpholine was also added to the reaction mixture).

(f) Compound 270f



A solution of aqueous NaOH (0.736 ml, 1N) was added at RT to a rapidly stirred solution of Compound 270e in THF (1ml). After 20 min, the solution was concentrated *in vacuo* then dried under high vacuum to afford 0.136 g (51%) of Compound 270f as a brown/green solid.

(g) Compound 270g



(mixture of diastereomers at \*)

Compounds 270f and 54 were reacted by a procedure analogous to that of Example 55 (DMF only used)

to give the title Compound 270g (white solid) as a mixture of diastereomers.

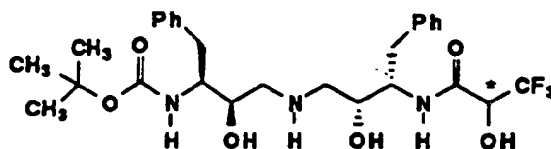
m.p. 174-176°C;  $[\alpha]_D = -30^\circ$  (c 0.1, MeOH)

Mass spec: HRMS  $C_{35}H_{45}O_8N_4$ : 617.3328+;

5 calculat d 617.3339+,  $\Delta = 1.8$  ppm.

#### Example 271

10 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-1-(phenylmethyl)-3-[[2-hydroxy-4-phenyl-3-[(3,3,3-trifluoro-2-hydroxy-1-oxopropyl)amino]butyl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester (isomer A) (Compound 271)

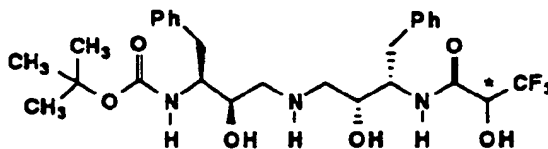


20 (single isomer at \*)

To a solution of trifluorolactic acid (0.107 g, 0.75 mmol, prepared as described in Burstein, *Can. J. Chem.*, 39, 1848 (1961)), HOBt monohydrate (0.135 g, 0.88 mmol) in 2.1 mL dry DMF at RT was added in succession N-methylmorpholine (0.163 mL, 1.49 mmol), Compound 54 (0.3 g, 0.68 mmol) and EDCI hydrochloride (0.143 g, 0.75 mmol). The resulting mixture was stirred at RT for 16 h, concentrated, and the residue partitioned between EtOAc and sat.  $NaHCO_3$ . The organic layer was dried ( $MgSO_4$ ), concentrated, and the crude product was purified by flash chromatography (silica gel/ $CH_2Cl_2$  to  $CH_2Cl_2$ -MeOH- $NH_4OH$  90:10:1, stepwise gradient) affording 0.21 g (54%) of a mixture of the two diastereomeric products. This mixture was subjected to preparative HPLC (Waters Prep Nova-Pack HR C18, 6 micron, 30X300 mm; eluent: MeOH-water-TFA 20:80:0.05 to 90:10:0.05; UV 254 nm). The desired fractions containing the faster eluting component on C18 were made basic with sat.  $NaHCO_3$ , concentrated, and the residue partitioned between EtOAc/brine. The organic phase was dried ( $MgSO_4$ ), concentrated, and the resulting solid was triturated from 5:1 pentane- $Et_2O$  to afford 51 mg (13%) of the title Compound 271 as a white solid. m. p. 160-163°C;  $[\alpha]_D = +2.25^\circ$  (c = 0.2, MeOH).  
35 High resolution Mass Spec.:  $(M+H)^+ = 570.2809$ , theoretical:  $(M+H)^+ = 570.2791$  ( $\Delta$  3.1 ppm error).

#### Example 272

40 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-1-(phenylmethyl)-3-[[2-hydroxy-4-phenyl-3-[(3,3,3-trifluoro-2-hydroxy-1-oxopropyl)amino]butyl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester (isomer B) (Compound 272)



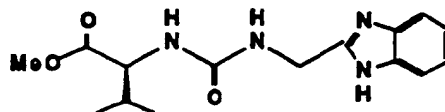
50 (single isomer at \*)

Compound 272 (white solid), the diastereomer of Compound 271, was isolated by preparative HPLC (work up of the fraction from the slower moving peak) as described in Example 271.  
55 m.p. 127-130°C;  $[\alpha]_D = +5.0^\circ$  (c = 0.3, MeOH).  
High resolution mass spectrum:  $(M+H)^+ = 570.2786$ , theoretical:  $(M+H)^+ = 570.2791$  ( $\Delta$  0.9 ppm error).

## Example 273

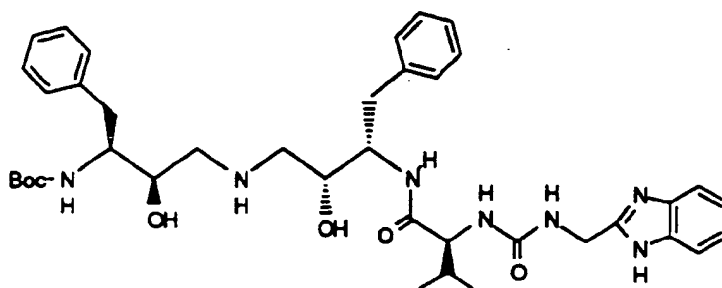
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[[[(1H-Benzimidazol-2-ylmethyl)amino]carbonyl]-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-L-valinamide (Compound 273b)

## (a) Compound 273a



2-Aminomethylbenzimidazole and Compound 245b were reacted by a procedure analogous to that of Example 245c to give Compound 273a.

## (b) Compound 273b



Compounds 273a and 54 were reacted by a two-step procedure analogous to that used for the conversion of Compound 70b to Compound 70d (DMF only; no N-methylmorpholine was added) to give the title Compound 273b (white solid) along with its valine diastereomer Compound 274. The diastereomers were separated on a 30 ml silica column eluting with 2-8% MeOH/CH<sub>2</sub>Cl<sub>2</sub> which was increased in 0.5% units with 0.1% NH<sub>4</sub>OH.

TLC(SiO<sub>2</sub>)R<sub>f</sub> = 0.40 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH:

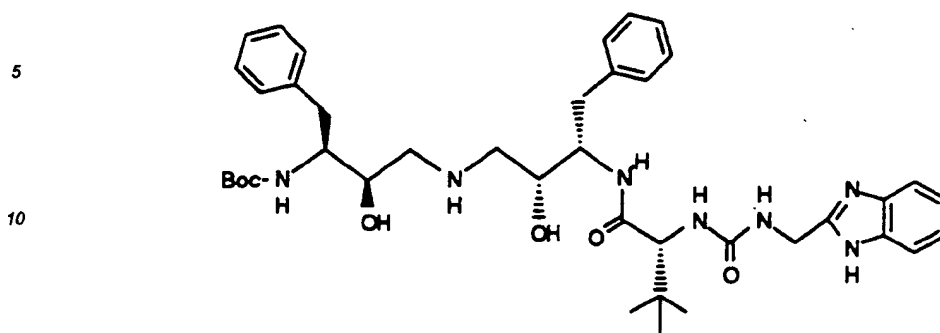
NH<sub>4</sub>OH 90:10:1)

m.p. 182-186°C (dec); [α]<sub>D</sub> = -22° (c = 0.25, MeOH)

Analysis Calcd. for: C <sub>39</sub> H <sub>53</sub> N <sub>7</sub> O <sub>6</sub> · 2.5 H <sub>2</sub> O			
	C, 61.57	H, 7.68	N, 12.89
Found:	C, 61.23	H, 7.33	N, 12.78.

## Example 274

Preparation of [1S\*,2R\*(2R\*,3S\*)]-N<sup>2</sup>-[[[(1H-Benzimidazol-2-ylmethyl)amino]carbonyl]-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-D-valinamide (Compound 274)



15 Compound 274 (white solid) was isolated as the slower moving isomer by the procedure described in Example 273b.

TLC(SiO<sub>2</sub>)R<sub>f</sub> = 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH 90:10:1)

m.p. 186-189°C (dec); [α]<sub>D</sub> = -10.5° (c = 0.25, MeOH)

20

Analysis Calcd. for: C <sub>39</sub> H <sub>53</sub> N <sub>7</sub> O <sub>8</sub> · 2.4 H <sub>2</sub> O			
	C, 61.77	H, 7.67	N, 12.93
Found:	C, 61.54	H, 7.28	N, 13.03

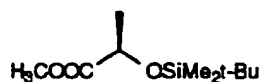
25

### Example 275

30 Preparation of [1S-(1R\*,2S\*), (S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 2-hydroxy-1,1-dimethylpropyl ester (Compound 275h)

#### (a) Compound 275a

35

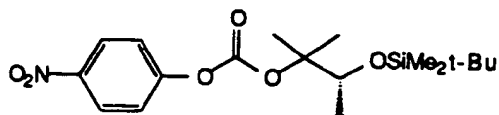


40

Compound 275a was prepared from (R)-methyl lactate by a procedure analogous to that of Example 232a.

#### (b) Compound 275b

45

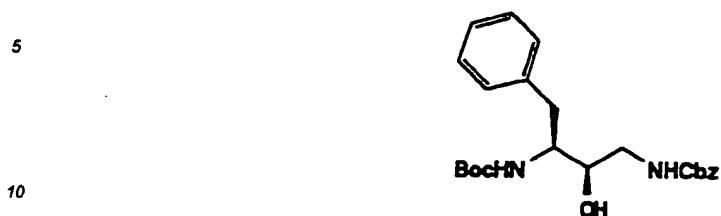


50

Compound 275a was converted to Compound 275b by a two-step procedure analogous to that used for the conversion of Compound 149b to Compound 149d.

55

**(c) Compound 275c**



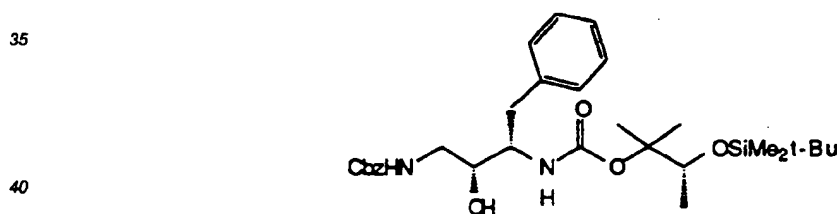
Compound 16b was reacted with benzylchloroformate by a procedure analogous to that used in Example 122 (reaction run at 0°C for 2 h) to give Compound 275c.

**(d) Compound 275d**



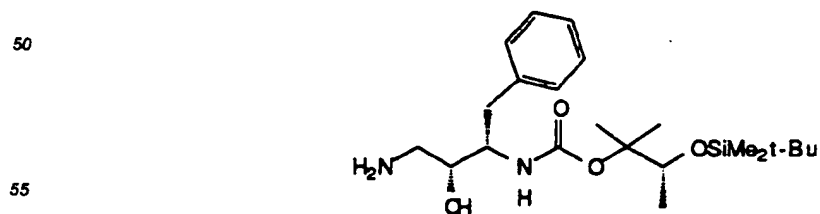
Solid Compound 275c (1.21 g; 2.91 mmol) was added to a saturated solution of HCl gas in 45 ml of EtOAc at 0°C. The reaction was stoppered and stirred for 3 h at 0°C. The solution was purged with N<sub>2</sub> for 15 min and the volatiles were removed *in vacuo* to afford 1.03 g (~100%; contained trace solvent) of Compound 275d as a white solid.

**(e) Compound 275e**



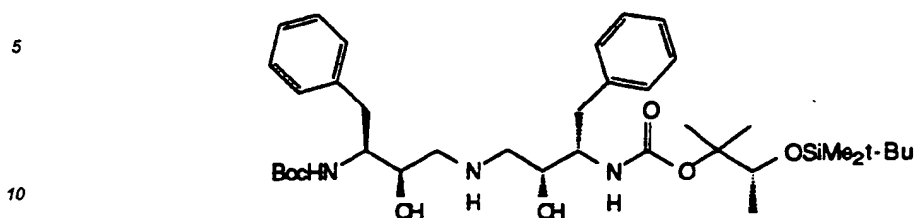
Compounds 275b and 275d were reacted by a procedure analogous to that of Example 161e to give Compound 275e.

**(f) Compound 275f**

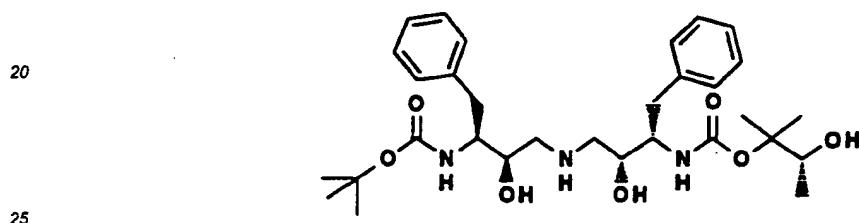


Compound 275e was converted to Compound 275f by a procedure analogous to that of Example 61.



(g) Compound 275g

Compounds 1b(i) and 275f were reacted by a procedure analogous to that of Example 4b to give Compound 275g.

(h) Compound 275h

Compound 275g was converted to the title Compound 275h (white solid) by a procedure analogous to that of Example 162.

m.p. 77-87°C. (dec.);  $[\alpha]_D^{25} = -8.5^\circ$  (c 0.27, MeOH).

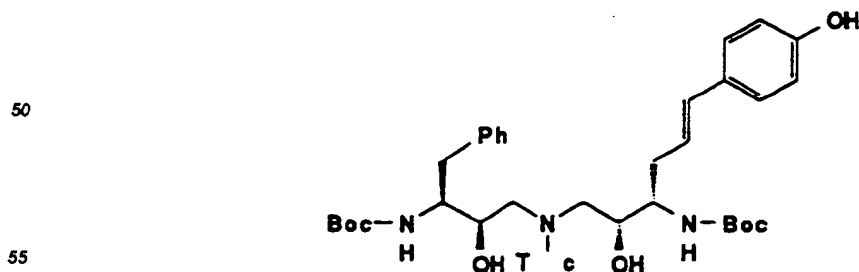
Mass Spec. FAB: M+H= 574 (M+H)

Analysis calc. for  $C_{31}H_{47}N_3O_7 \cdot 0.64 H_2O$ :

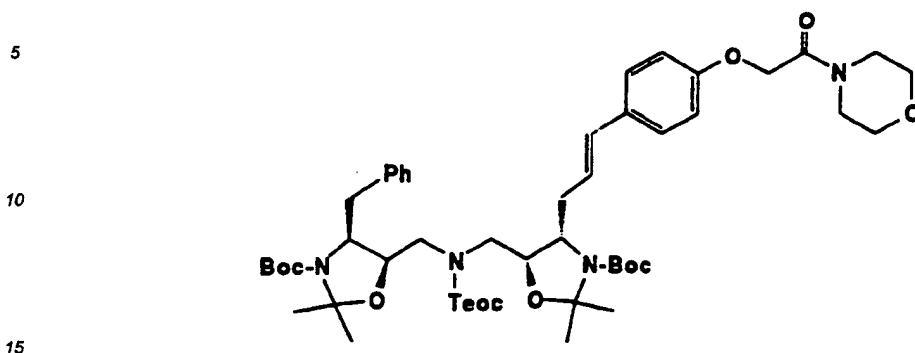
	C, 63.62;	H, 8.31;	N, 7.18;
Found:	C, 63.57;	H, 8.33;	N, 7.23.

Example 276

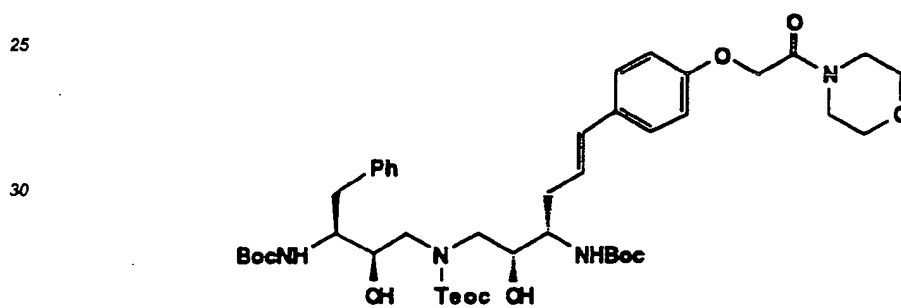
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-6-[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]-5-hexenyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 276d)

(a) Compound 276a

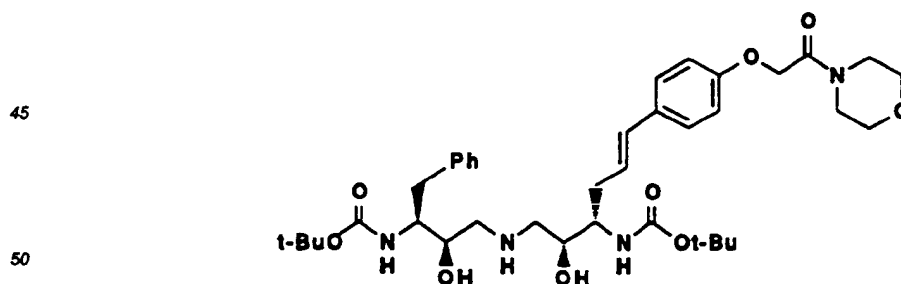
Compound 235e was converted to Compound 276a by a procedure analogous to that of Example 18.

(b) Compound 276b

Compound 276a and 4-(2-bromoacetyl)morpholine (J. Med. Chem., 35, 1685 (1992)) were converted to Compound 276b by a two-step procedure analogous to that used for the conversion of Compound 20 to Compound 173.

(c) Compound 276c

Compound 276b was converted to Compound 276c by a two-step procedure analogous to that of Example 177.

(d) Compound 276d

Compound 276c was converted to the title Compound 276d (white solid) by a procedure analogous to that of Example 21.

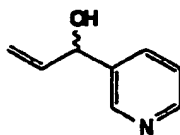
m.p. 115-116°C;  $[\alpha]_D^{25}$  (365) = -27.1° (c 0.14, MeOH).  
Mass Spec. (FAB): 713<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calcd. for  $C_{38}H_{56}N_4O_9$ :

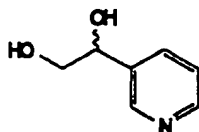
	C, 64.00;	H, 7.92;	N, 7.86.
Found:	C, 63.78;	H, 7.93;	N, 8.08.

**Example 277**

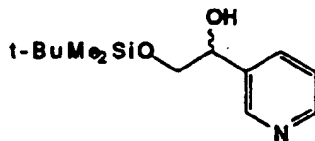
**Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-2-hydroxy-1-(3-pyridinyl)ethyl ester (Compound 277e)**

**(a) Compound 277a**

To a 0°C solution of vinyl magnesium bromide (41.0 mL of a 1.0 M solution in THF) was added dropwise over 1 h a solution of pyridine 3-carboxaldehyde (4.00 g, 37.3 mmol) in THF (50 mL). The resulting orange-yellow solution was allowed to warm to RT and stirred for 24 h under argon. The reaction mixture was cooled to 0°C, then was quenched by slow addition of aqueous  $NH_4Cl$  (55 mL of a 1 M solution). EtOAc was added and the resulting emulsion was filtered through Celite in a sintered glass funnel under vacuum. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated *in vacuo* to give a red oil which was purified on silica gel (500 mL) using a stepwise gradient from 1:1 to 1:5 hexanes:ethyl acetate as eluent to give Compound 277a (3.89 g; 77%) as a pale yellow oil.

**(b) Compound 277b**

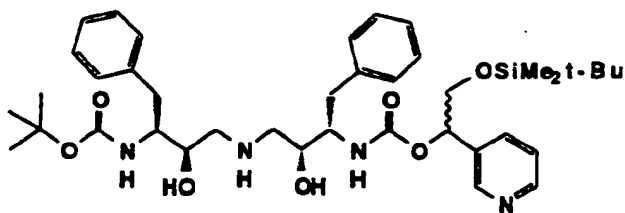
Ozone was bubbled through a solution of 1.00 g (7.40 mmol) of Compound 277a in 25 mL of  $CH_3OH$  at -78°C for 20 min. After purging with  $N_2$  and warming to 0°C, the reaction mixture was diluted with 3 mL of  $H_2O$  and  $NaBH_4$  (420 mg, 11.1 mmol) was added. The mixture was stirred for 30 min at 0°C and for 1 h at RT then quenched by the addition of 10 mL of saturated  $NH_4Cl$ . The pH was adjusted to 4 with 20 mL of 1M HCl, and the reaction mixture was concentrated *in vacuo*. Flash chromatography on silica gel [2%  $CH_3OH/CH_2Cl_2$ , then 3-10%  $CH_3OH/CH_2Cl_2$  (with 1.0%  $NH_4OH$ )] provided 717 mg (70%) of Compound 277b.

**(c) Compound 277c**

To a solution of 677 mg (4.86 mmol) of Compound 277b in 20 mL of dry  $CH_2Cl_2$  at 0°C were added 0.75 mL (5.4 mmol) of  $Et_3N$ , 30 mg DMAP, and 769 mg (5.10 mmol) of t-butyldimethylsilylchloride. The reaction mixture was warmed to RT over 4 h and then stirred for 4 days. The reaction mixture was diluted with 75 mL of EtOAc, and washed with saturated  $NaHCO_3$  and brine. The organic layer was dried ( $Na_2SO_4$ ), filtered, and concentrated *in vacuo* to provide, after flash chromatography on silica gel (25-100% EtOAc-hexane), 1.12 g (91%)

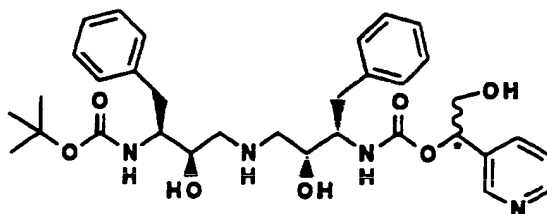
of Compound 277c.

(d) Compound 277d



Compounds 277c and 54 were reacted by a two-step procedure analogous to that used for the conversion of Compound 147b to Compound 147d to give Compound 277d.

(e) Compound 277e



(1:1 mixture of isomers at \*)

Compound 277d was converted to the title Compound 277e (white solid) by a procedure analogous to that of Example 162.

m.p. 75-85°C;  $[\alpha]_D^{25} = -13^\circ$  (c 0.28, CH<sub>3</sub>OH)

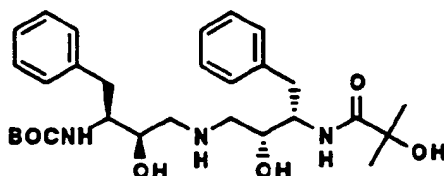
Mass Spec. 609 (M+H)<sup>+</sup>

Analysis Calcd. for C<sub>33</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub>·1.03 H<sub>2</sub>O:

	C, 63.18;	H, 7.40;	N, 8.93.
Found:	C, 63.28;	H, 7.28;	N, 8.83.

Example 278

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(2-hydroxy-2-methyl-1-oxopropyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 278)



Compound 54 and 2-hydroxyisobutyric acid were reacted by a procedure analogous to that of Example 269 to give the title Compound 278 (white solid).

m.p. 162-166°C ("softening" at 156-161°C);  $[\alpha]_{H_2O}^{25} = -2.9^\circ$  (c=0.99, CH<sub>3</sub>OH).

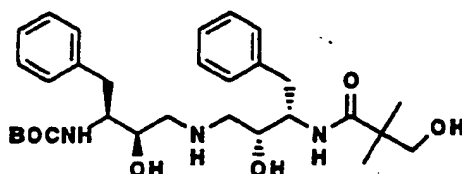
Mass Spec. (FAB), 530 (M+H)<sup>+</sup>

Analysis Calcd. for  $C_{29}H_{43}N_3O_6 \cdot 0.48 H_2O$ :

	C, 64.70;	H, 8.23;	N, 7.81.
Found:	C, 64.72;	H, 8.32;	N, 7.79.

**Example 279**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-(hydroxymethyl)-2-methyl-1-oxopropyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 279)



Compound 54 and 2,2-dimethyl-3-hydroxypropionic acid were reacted by a procedure analogous to that of Example 269 ( $CH_2Cl_2$  only used) to give the title Compound 279 (white solid).

m.p. 73-76°C ("softening" at 66-72°C);  $[\alpha]_D = +3.6^\circ$ ; (c=0.76,  $CH_3OH$ ).

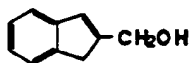
Mass Spec. (FAB), 544 ( $M+H^+$ )

Analysis Calcd. for  $C_{30}H_{45}N_3O_8 \cdot 0.29 H_2O$ :

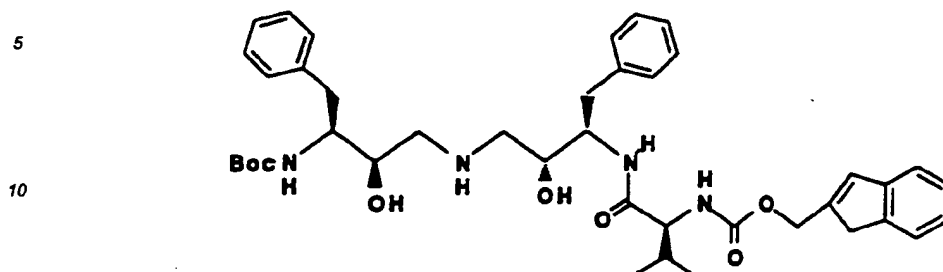
	C, 65.64;	H, 8.37;	N, 7.65.
Found:	C, 65.64;	H, 8.33;	N, 7.81.

**Example 280**

Preparation of [1R\*, 2S\* (2S\*, 3R\*)]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[[[(1H-inden-2-yl)methoxy]carbonyl]-L-valinamide (Compound 280b)

**(a) Compound 280a**

A solution of 2-carboethoxyindene (1.0 g, 6.24 mmol; see Treibs, *Chem. Ber.*, 93, 545 (1960)) in 15 ml of dry toluene was treated with 4 eq. of a 1 M solution of diisobutylaluminum hydride in toluene (24.96 ml) at RT. After 4 h at RT, the reaction was cooled in an ice-bath and MeOH was added. The mixture was filtered and the solvents evaporated yielding the crude product as a colorless oil which was purified by chromatography on silica column eluting with 60% EtOAc/hexane to afford 593 mg (77%) of Compound 280a as a colorless solid.

(b) Compound 280b

15 L-Valine and Compounds 280a and 54 were reacted by a three-step procedure analogous to that described for the conversion of Compound 171a to Compound 257c to give the title Compound 280b (colorless solid).  
 m.p. 148-154°C (dec);  $[\alpha]_D = -18.5^\circ$  (c 0.22, MeOH)  
 Mass Spec. (FAB): 715<sup>+</sup> (M+H)<sup>+</sup>

20 Analysis Calcd. for: C<sub>41</sub>H<sub>54</sub>N<sub>4</sub>O<sub>7</sub> + 0.75 H<sub>2</sub>O:

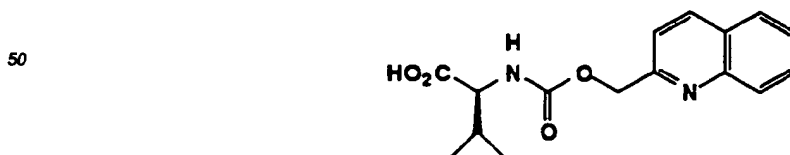
	C, 67.61;	H, 7.68;	N, 7.69
Found:	C, 67.62;	H, 7.52;	N, 7.68.

Example 281

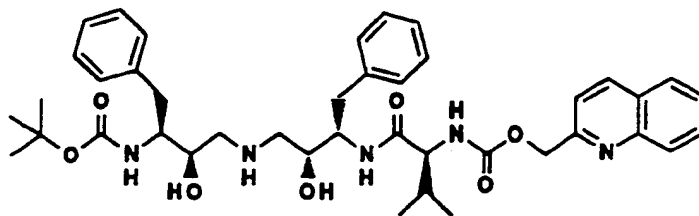
25 Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(2-quinolinyloxy)carbonyl]-L-valinamide (Compound 281c)

(a) Compound 281a

40 A solution of 7.25 mL (7.25 mmol; 1.0M in Et<sub>2</sub>O) of LiAlH<sub>4</sub> was diluted with 4 mL of dry Et<sub>2</sub>O and cooled to -60°C. To this was added, over 30 min, a solution of 1.15 g of methyl quinaldate in 7 mL of dry Et<sub>2</sub>O. The mixture was warmed to -25°C, stirred for 15 min, and treated with 10 mL of Et<sub>2</sub>O which was saturated with H<sub>2</sub>O. The mixture was warmed to 0°C and quenched by the addition of a solution of 360 mg of NaOH in 2 mL of H<sub>2</sub>O. The mixture was diluted with 100 mL of Et<sub>2</sub>O and washed with H<sub>2</sub>O and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo* to give crude material which was purified by flash chromatography on silica gel (25-100% EtOAc-hexane) to afford 445 mg (46%) of Compound 281a.

(b) Compound 281b

55 Compound 281a and L-valine were reacted by a two-step procedure analogous to that described for the conversion of Compounds 70a(i) and 70a(ii) to Compound 70c to give Compound 281b.

(c) Compound 281c

Compounds 281b and 54 were reacted by a procedure analogous to that of Example 55 (DMF only used) to give the title Compound 281c (white solid).

m.p. 177-190°C (dec.);  $[\alpha]_D = -12^\circ$  (c 0.33, CH<sub>3</sub>OH)

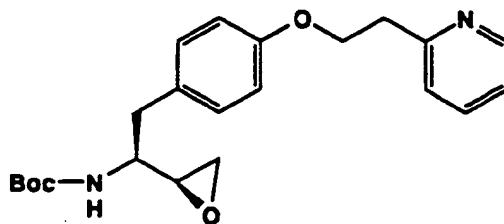
Mass Spec. 728 (M=H)<sup>+</sup>

Analysis Calcd. for: C<sub>41</sub>H<sub>53</sub>N<sub>5</sub>O<sub>7</sub> · 0.85 H<sub>2</sub>O:

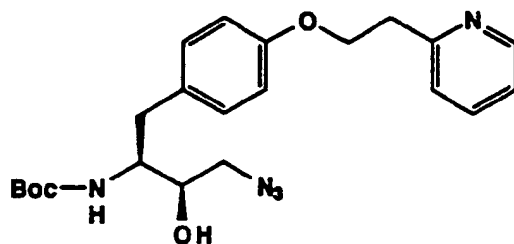
	C, 66.25;	H, 7.42;	N, 9.42
Found:	C, 66.10;	H, 7.28;	N, 9.57

Example 282

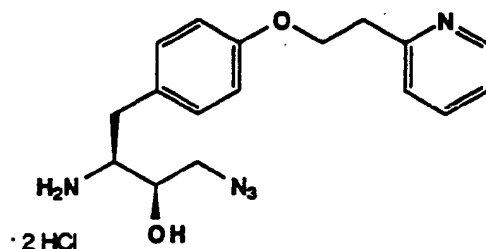
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester (Compound 282g)

(a) Compound 282a

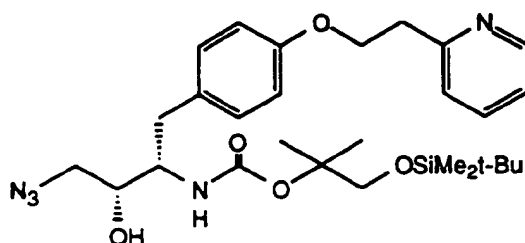
To a suspension of Compound 175c (400 mg, 1.43 mmol) in THF (1.5 mL) was added PPh<sub>3</sub> (0.564 g, 2.15 mmol), followed by 2-(2-hydroxyethyl)pyridine (256.5 mg, 2.15 mmol) and DEAD (0.374 g, 2.15 mmol). The resulting solution was stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography, eluting with EtOAc (10% to 100%)-hexane to afford Compound 282a (0.254 g, 45% yield).

(b) Compound 282b

To a solution of Compound 282a (200 mg, 0.52 mmol) in MeOH (ca. 8 mL) was added NaN<sub>3</sub> (101.45 mg, 1.56 mmol) and NH<sub>4</sub>Cl (50 mg, 0.93 mmol) and the mixture heated at reflux for 18 h. The solution was cooled to RT, and the solvent removed under vacuum. The residue was taken in EtOAc and washed with H<sub>2</sub>O and brine. The combined organic phase was dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to yield Compound 282b (187 mg, 71%) as a gummy white residue.

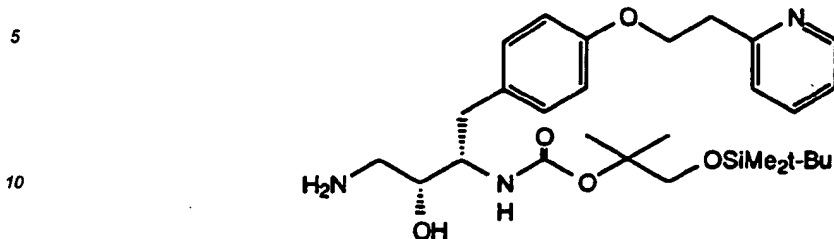
(c) Compound 282c

Compound 282b (180 mg, 0.421 mmol) in 4M HCl in dioxane (3.36 mL) was stirred at RT for 1 h, and concentrated *in vacuo* to yield a yellow residue which was azeotroped from CHCl<sub>3</sub> and then toluene to yield Compound 282c as a foamy yellow solid (197 mg, ca. 100% yield, crude).

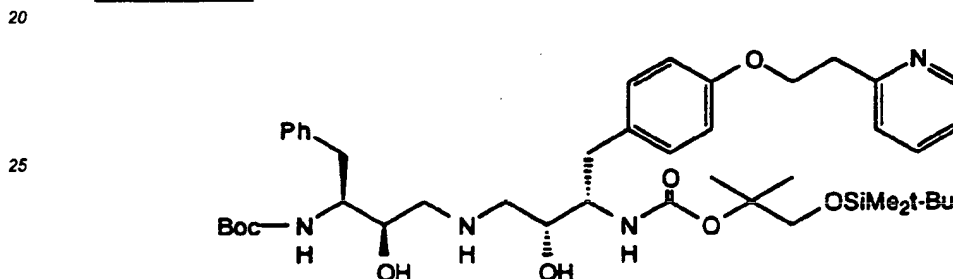
(d) Compound 282d

To Compound 282c (195 mg, 0.595 mmol) in DMF (0.5 mL) was added *i*-Pr<sub>2</sub>NEt (0.72 mL, 4.16 mmol), followed by a solution of the Compound 161d (242 mg, 0.655 mmol) in DMF (ca. 0.5 mL) and the mixture stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and the residue taken in EtOAc and washed with 1:1 saturated NaHCO<sub>3</sub>:brine. The combined organic layer was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to yield a yellow gummy residue which was purified by flash chromatography, eluting with CH<sub>3</sub>OH (1% to 30%)-CH<sub>2</sub>Cl<sub>2</sub> to afford Compound 282d (250 mg, 75% yield) as a yellow solid.



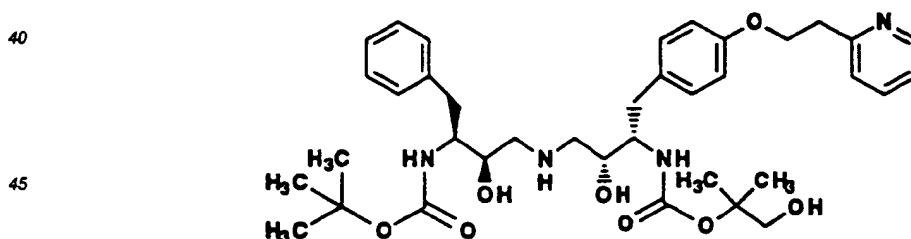
( ) Compound 282e

15 To a solution of Compound 282d (235 mg, 0.421 mmol) in THF (2.5 mL) was added H<sub>2</sub>O (12  $\mu$ L), followed by triphenylphosphine (122 mg, 0.463 mmol) and the mixture stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo*, and purified on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH (99:1:0.02 to 85:15:0.1) to afford Compound 282e (145 mg, 65% yield) as a gummy white solid.

(f) Compound 282f

35 To a solution of Compound 282e (134 mg, 0.252 mmol) in DMF (0.5 mL) was added the Compound 1b(i) (66.36 mg, 0.252 mmol) and the mixture heated at 110°C for 6 h, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH (99:1:0.02 to 90:10:1) to afford Compound 282f (114 mg, 57% yield) as a white residue.

TLC(SiO<sub>2</sub>) R<sub>f</sub> = 0.22 (9:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:aq. NH<sub>4</sub>OH - Rydon)

(g) Compound 282g

50 Compound 282f (114 mg, 0.143 mmol) in a mixture of HOAc:THF:H<sub>2</sub>O (3:1:1, 1.5 mL) was stirred at RT for 40 h, and then heated at 50°C for 4 h. The reaction mixture was concentrated *in vacuo* and the residue purified by silica gel chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH (97.5:2.5:0.025 to 90:10:1) to afford the title Compound 282g (50 mg, 51% yield) as a foamy white solid.

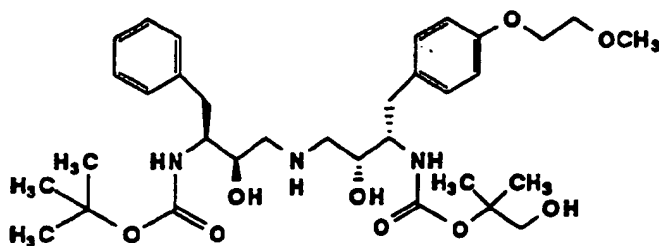
m.p. 106-108°C; [ $\alpha$ ]<sub>D</sub> = -4.0° (c = 0.2, CH<sub>3</sub>OH).

55

Analysis for $C_{37}H_{52}N_4O_8 \cdot 0.84 H_2O$			
Calculated:	C, 63.85;	H, 7.77;	N, 8.05.
Found:	C, 63.86;	H, 7.58;	N, 8.04.

### Example 283

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-(2-methoxyethoxy)phenyl]methyl]propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester (Compound 283)



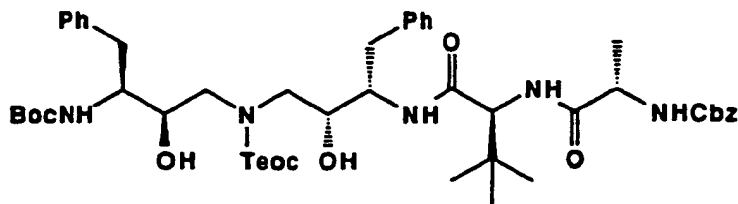
Compound 175c and 2-methoxyethanol were converted to the title Compound 283 (white solid) by a seven-step procedure analogous to that used in Example 282.  
m.p. 118-120°C;  $[\alpha]_D = -3.90^\circ$  (c = 0.2,  $CH_3OH$ ).

Analysis for $C_{33}H_{51}N_3O_9 \cdot 0.38 H_2O$			
Calculated:	C, 61.87;	H, 8.14;	N, 6.56.
Found:	C, 61.88;	H, 8.08;	N, 6.55.

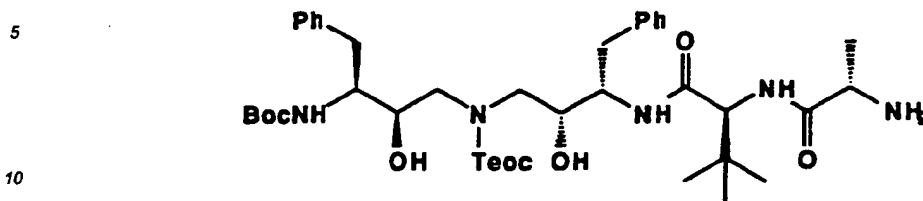
### Example 284

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(N-formyl-L-alanyl)-3-methyl-L-valinamide (Compound 284d)

#### (a) Compound 284a

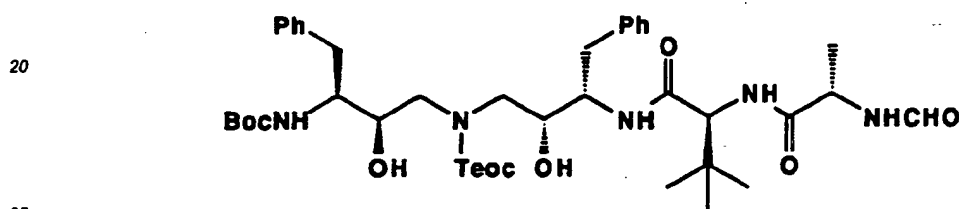


Compound 263b and N-carbobenzoxy-L-alanine were reacted by a procedure analogous to that of Example 51 to give Compound 284a.

(b) Compound 284b

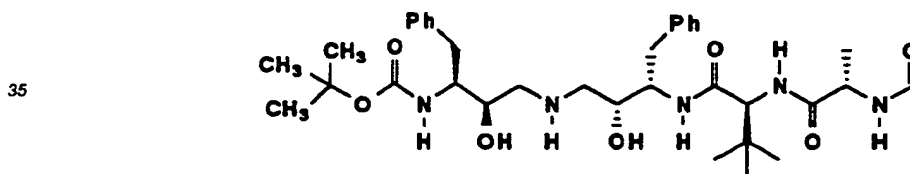
Compound 284a was converted to Compound 284b by a procedure analogous to that of Example 61 (EtOH was used instead of MeOH).

15

(c) Compound 284c

Compound 284b was reacted with formic acetic anhydride by a procedure analogous to that of Example 129 to give Compound 284c.

30

(d) Compound 284d

40 Compound 284c was converted to the title Compound 284d (white solid) by a procedure analogous to that of Example 21.

m.p. 167-170°C,  $[\alpha]_D = -25.7^\circ$  (MeOH, C = 0.6).

Mass Spec. 656 (M + H)<sup>+</sup>

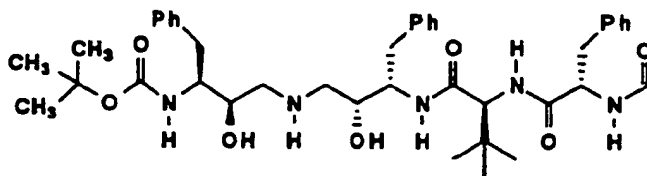
45

Example 285

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(N-formyl-L-phenylalanyl)-3-methyl-L-valinamide Compound 285

50

55



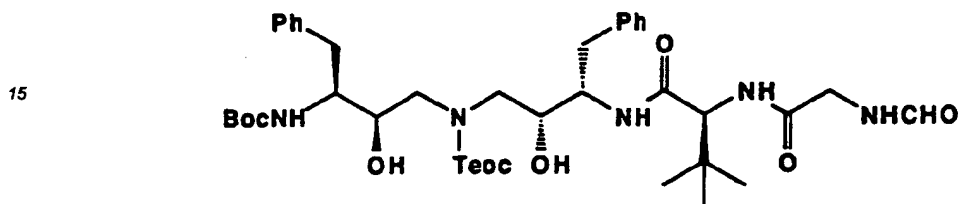
Compound 263b and N-carbobenzyl-L-phenylalanine were converted to the title Compound 285 (white solid) by a four-step procedure analogous to that described in Example 284.

m.p. 117-119°C,  $[\alpha]_D = -9.6^\circ$  (MeOH, c 1.12).  
Mass Spec. 732 (M+H)<sup>+</sup>

5 Exempl 286

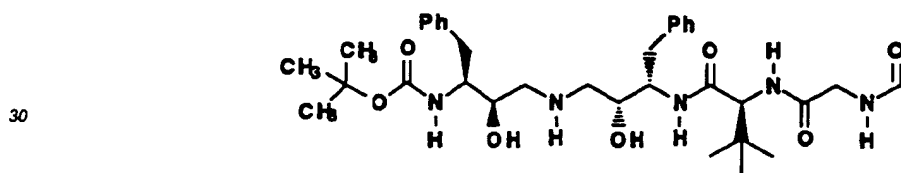
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(N-formylglycyl)-3-methyl-L-valinamide (Compound 286b)

10 (a) Compound 286a



20 Compound 263b and N-formylglycine were reacted by a procedure analogous to that of Example 51 to give Compound 286a.

25 (b) Compound 286b



35 Compound 286a was converted to the title Compound 286b (white solid) by a procedure analogous to that of Example 21.  
m.p. 180-183° C

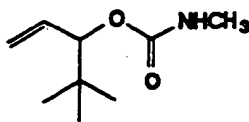
Example 287

40 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[3,3-Dimethyl-2-[[[(methylamino)carbonyl]oxy]-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid, 1,1-dimethylethyl ester (Compound 287d)

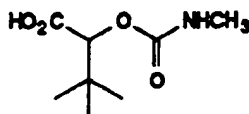
45 (a) Compound 287a



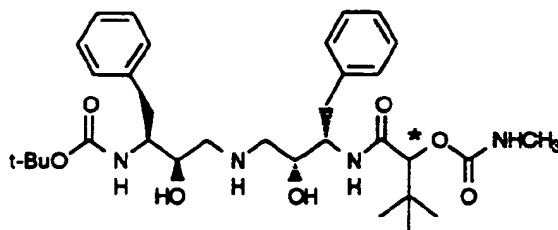
Vinyl magnesium bromide was added to pivaldehyde by a procedure analogous to that of Example 277a to give Compound 287a as a yellow-orange oil.

(b) Compound 287b

To a 0°C suspension of THF-washed NaH (0.116 g of an 80% oil dispersion) in anhydrous THF (5 mL) was added dropwise a solution of Compound 287a (0.400 g; 3.50 mmol) in THF (10 mL). The reaction mixture was allowed to warm to RT and stirred for 1 h. After recooling to 0°C, a solution of methyl isocyanate (0.25 mL; 4.20 mmol) in THF (1.5 mL) was added dropwise. The reaction was allowed to warm to RT and stirred for 4 h. Aqueous NH<sub>4</sub>Cl (10 mL of a 1 M solution) and EtOAc (20 mL) were added. The aqueous layer was saturated with NaCl and extracted with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give Compound 287b (0.302 g; 50%) as a yellow oil.

(c) Compound 287c

Compound 287b was converted to Compound 287c by a procedure analogous to that of Example 238b.

(d) Compound 287d

(1:1 isomeric mixture at \*)

Compound 287c was converted to the title Compound 287d (white solid) by a procedure analogous to that of Example 93f.

m.p. = 85°-89°C (softens at 65°-70°C); [ $\alpha$ ]<sub>D</sub> = -5.8° (c 0.12, MeOH)

Mass Spec. (M + H)<sup>+</sup> = 615

Analysis Calculated for C<sub>33</sub>H<sub>50</sub>N<sub>4</sub>O<sub>7</sub>·0.80 H<sub>2</sub>O:

C, 63.00; H, 8.27; N, 8.91

Found: C, 63.00; H, 8.20; N, 8.63

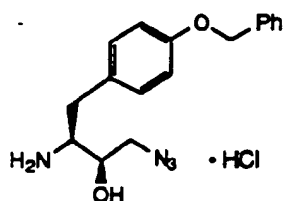
Example 288

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N<sup>2</sup>-[[[(2-Benzoxazolyl)methoxy]carbonyl]-N-[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[(4-hydroxyphenyl)methyl]pyrrolidine]-L-valinamide (Compound 288f)

(a) Compound 288a

5

10



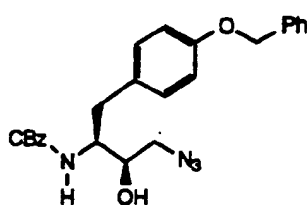
Compound 175b was converted to Compound 288a by a two-step procedure analogous to that described for the conversion of Compound 282a to Compound 282c.

15

(b) Compound 288b

20

25



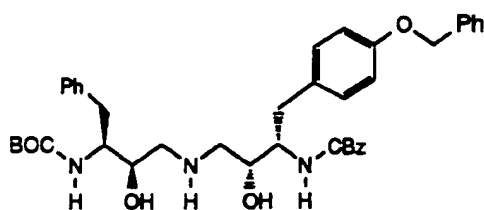
Compound 288a was converted to Compound 288b by a procedure analogous to that of Example 122 except that benzyloxychloroformate was used.

30

(c) Compound 288c

35

40



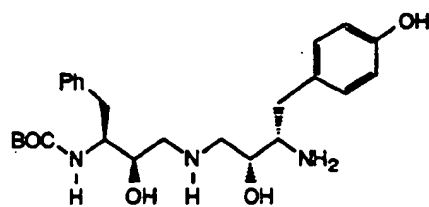
Compounds 288b and 1b(i) were converted to Compound 288c by a two-step procedure analogous to that used for the conversion of Compound 282d to Compound 282f (except that the second step was performed in i-PrOH at 80°C).

45

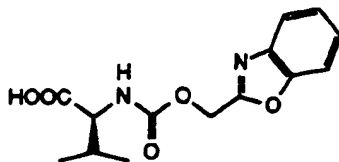
(d) Compound 288d

50

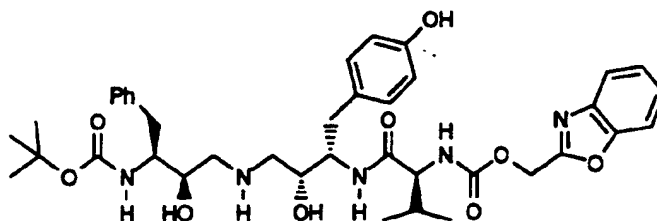
55



Hydrogenation (balloon) of 120 mg (0.175 mmole) of Compound 288c in 10 ml of Me OH over 30 mg of 10% Pd/C catalyst afforded 80 mg (0.174 mmole, 100%) of Compound 288d as a solid foam.

(e) Compound 288e

Compound 288e was prepared as described in Example 171.

(f) Compound 288f

Compounds 288d and 288e were reacted by a procedure analogous to that of Example 93f to give the title Compound 288f (white solid).

m.p. 175-177°C;  $[\alpha]_D = -20.1$  (c. 0.92, MeOH)

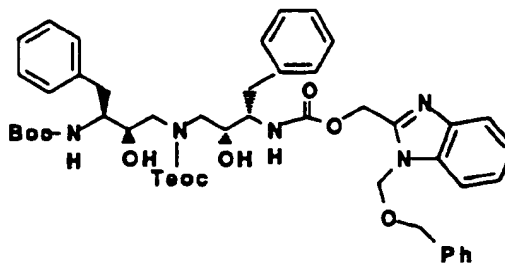
Mass Spec.:  $(M+H)^+$  734<sup>+</sup>

Analysis Calc. for  $C_{39}H_{51}N_5O_9 \cdot 0.33 H_2O$ :

	C, 63.32;	H, 7.04;	N, 9.47.
Found:	C, 63.32;	H, 7.03,	N, 9.27.

Example 289

Preparation of [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, (1H-benzimidazol-2-yl)methyl 1,1-dimethylethyl ester (Compound 289e)

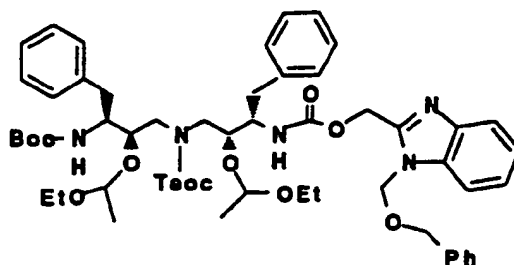
(a) Compound 289a

Compounds 93c and 48 were reacted by a procedure analogous to that of Example 149e (DMF used) to give Compound 289a.

(b) Compound 289b

5

10



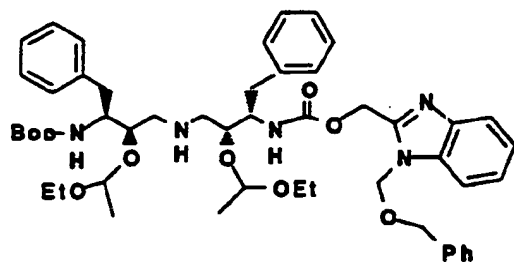
15

Compound 289a was converted to Compound 289b by a procedure analogous to that of Example 140a.

(c) Compound 289c

20

25



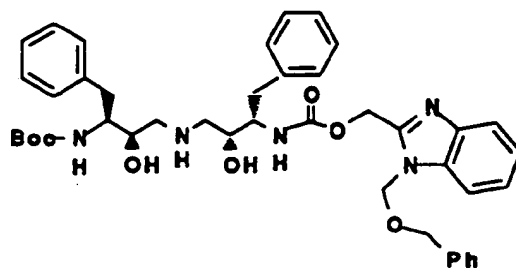
30

Compound 289b was converted to Compound 289c by a procedure analogous to that of Example 21.

(d) Compound 289d

35

40



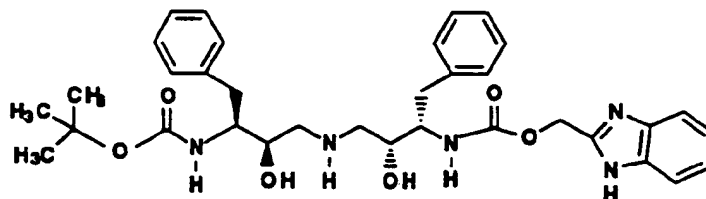
45

Compound 289c was converted to Compound 289d by a procedure analogous to that of Example 140e.

(e) Compound 289e

50

55



Compound 289d was converted to the title Compound 289e (white solid) by a procedure analogous to that of Example 7 (1 q. of hydrazine mon hydrat was added).



m.p. 95-105°C;  $[\alpha]_D^{25} = -9.3^\circ$  (c = 0.2, CH<sub>3</sub>OH).  
 Mass Spec. (FAB) (M + H)<sup>+</sup> = 618

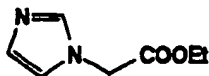
Analysis calc. for C<sub>34</sub>H<sub>43</sub>N<sub>5</sub>O<sub>8</sub> · 1.02H<sub>2</sub>O:

	C, 64.19;	H, 7.14;	N, 11.01;
Found:	C, 64.39;	H, 6.89;	N, 10.81.

#### Example 290

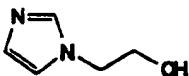
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(1H-imidazol-1-yl)-ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 290d)

##### (a) Compound 290a



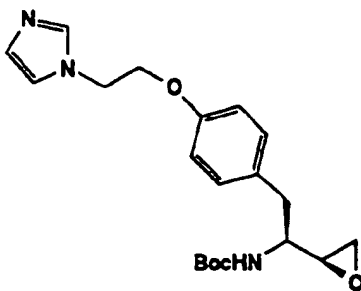
A mixture of imidazole (2 g; 29 mmol), ethyl bromoacetate (3.2 ml; 29 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.1 g; 58 mmol) in 30 ml of DMF was heated to 65°C for 18 h. After cooling to RT, the reaction mixture was filtered through a glass-fritted funnel and the filtrate was concentrated *in vacuo*. The residue was purified on a 5 x 15 cm silica gel column, using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> as the mobile phase to afford 2.10 g (49%) of Compound 290a as a light orange oil.

##### (b) Compound 290b

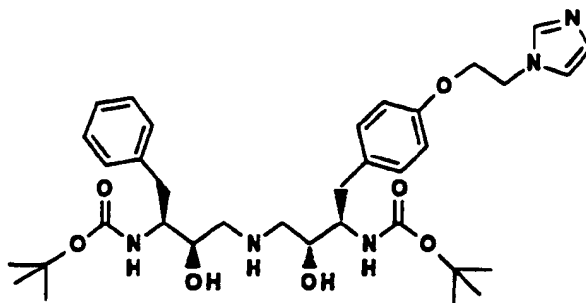


Compound 290a was converted to Compound 290b by a procedure analogous to that of Example 281a.

##### (c) Compound 290c



Compounds 290b and 175c were reacted by a procedure analogous to that of Example 282a to give Compound 290c.

(d) Compound 290d

Compounds 290c and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 290d (white solid).

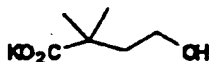
m.p. 130-135°C (dec.);  $[\alpha]_{365} = -14.1^\circ$  (0.33, MeOH).

Mass Spec. CI: (M+H) 654

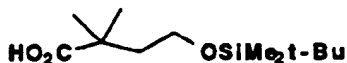
Analysis calc. for $C_{35}H_{51}N_5O_7 \cdot 0.52 H_2O$ :			
	C, 63.38;	H, 7.91;	N, 10.56;
Found:	C, 63.31;	H, 7.97;	N, 10.63.

Example 291

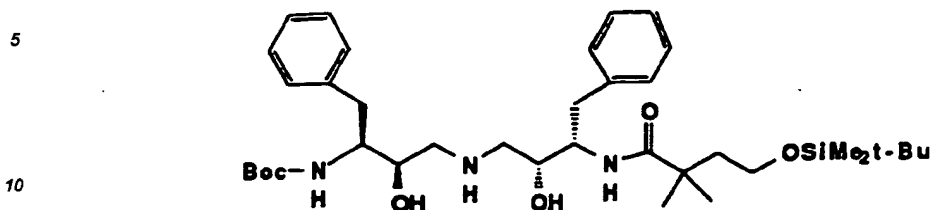
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(4-hydroxy-2,2-dimethyl-1-oxobutyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 291d)

(a) Compound 291a

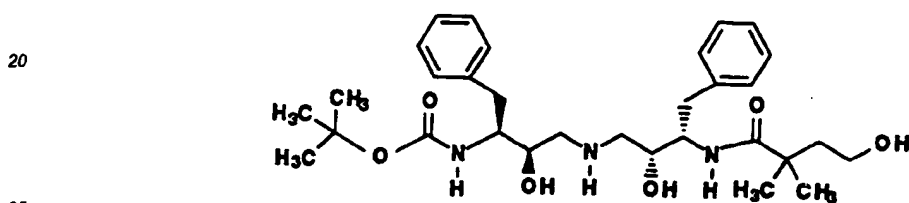
Compound 291a was prepared as described in U.S. Patent No. 4,732,902.

(b) Compound 291b

To a solution of Compound 291a (2.0 g, 11.76 mmol) in DMF was added t-butyldimethylsilyl chloride (10.635 g, 70.56 mmol) and imidazole (8.006 g, 117.6 mmol). The resulting mixture was stirred at RT for 24 h. MeOH (100 mL) was added and the reaction mixture was stirred at RT for 24 h. The mixture was diluted with EtOAc and washed with 10% citric acid (until aqueous phase had pH=2) followed by H<sub>2</sub>O and brine. The organic phase was separated, dried (MgSO<sub>4</sub>) and concentrated. The crude residue was purified by flash chromatography on silica gel eluting with 90:9:1 followed by 80:19:1 hexane-EtOAc-HOAc to afford Compound 291b (1.8 g, 62%) as a colorless oil.

(c) Compound 291c

Compounds 291b and 54 were reacted by a procedure analogous to that of Example 55 to give Compound 291c.

(d) Compound 291d

Compound 291c was converted to Compound 291d (white solid) by a procedure analogous to that of Example 162.

m.p. 70-74°C (softening at 60-65°C);  $[\alpha]_D^{25} = -1.2^\circ$  (c = 1.0, CH<sub>3</sub>OH).

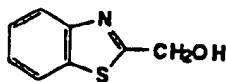
Mass Spec. (FAB) (M + H)<sup>+</sup> = 558

Analysis for C<sub>31</sub>H<sub>47</sub>N<sub>3</sub>O<sub>8</sub> · 0.35H<sub>2</sub>O:

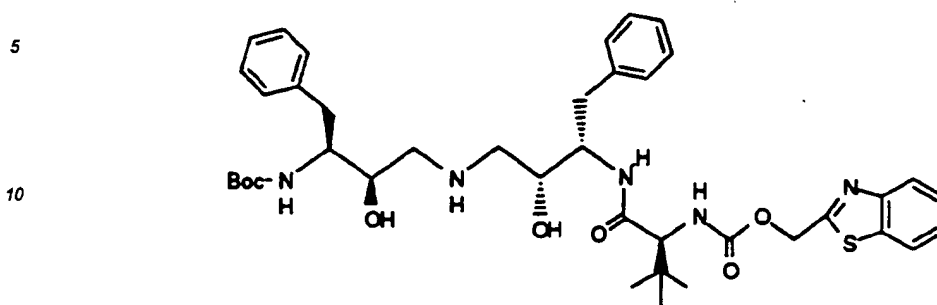
Calculated:	C, 66.01;	H, 8.52;	N, 7.45.
Found:	C, 65.91;	H, 8.55;	N, 7.55.

Example 292

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-benzothiazolyl)methyl ester (Compound 292b)

(a) Compound 292a

2-Aminothiophenol and glycolic acid were reacted by a procedure analogous to that of Example 171a to give Compound 292a.

(b) Compound 292b

15

Compound 292a and L-tert-leucine were reacted by a three-step procedure analogous to that used for the conversion of Compound 171a to Compound 257c to give the title Compound 292b (colorless solid).  
 m.p. 148-154°C (dec);  $[\alpha]_D^{25} = -14.5^\circ$  (c = 0.25, MeOH).  
 Mass Spec. (FAB):  $(M+H)^+ = 748^+$

20

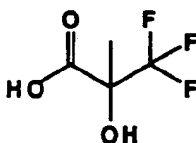
Analysis Calcd. for  $C_{40}H_{53}N_5SO_7 \cdot 1.78 H_2O$ :

	C, 61.60;	H, 7.31;	N, 8.98;	S, 4.11
Found:	C, 61.62;	H, 6.96;	N, 8.96;	S, 4.01

Example 293

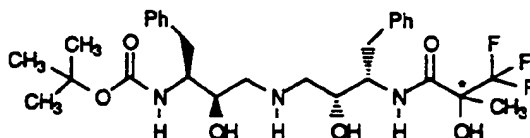
30

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[2-hydroxy-1-oxo-2-(trifluoromethyl)propyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethylester (isomer A) (Compound 293b)

(a) Compound 293a

45

1,1,1-Trifluoroacetone cyanohydrin (5 g, 39.4 mmol) was added to 5 mL conc.  $H_2SO_4$  with stirring at RT. The mixture was heated at 120°C for 15 min and 20 mL ice cold water was added. After refluxing for 15 h, the reaction was cooled to RT, saturated with  $Na_2SO_4$  and extracted with  $Et_2O$ . The combined  $Et_2O$  extracts were dried ( $MgSO_4$ ), the  $Et_2O$  distilled off with a vigreux column at atmospheric pressure and the residue sublimed (0.5 mm at 150-200°C) to afford 4.3 g (69%) of the Compound 293a as a white solid.

(b) Compound 293b

To a solution of Compound 293a (117.5 mg, 0.75 mmol) and HOBT monohydrate (0.135 g, 0.88 mmol) in 2 mL dry DMF at RT was added in succession Compound 54 (0.3 g, 0.68 mmol), N-methylmorpholine (0.1634

mL, 1.49 mmol), and EDCI hydrochloride (0.1434 g, 0.75 mmol). The resulting mixture was stirred at RT for 14 h, concentrated, and the residue partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, concentrated, and the crude product was purified by flash chromatography (silica gel/CH<sub>2</sub>Cl<sub>2</sub> to CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH 90:10:1, continuous gradient) affording 0.3 g (76%) of a mixture of the two diastereomeric products (at \*). This mixture was subjected to prep. HPLC (Waters Prep Nova-Pack HR C18, 6 micron, 40X300 mm; eluent: MeOH-water-TFA 50:50:0.05 to 100:0:0.05; UV 254 nm). The desired fractions containing the faster eluting component were made basic with sat. NaHCO<sub>3</sub>, concentrated, and the residue partitioned between EtOAc/1:1 brine-sat. NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to afford 100 mg (25%) of the title Compound 293b (single diastereomer) as a white solid.

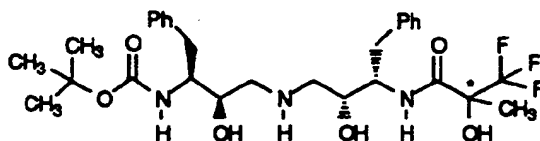
m.p. 203-204°C; [ $\alpha$ ]<sub>D</sub> = +1.5° (c = 1.2, MeOH).  
Mass Spec. 584 (M+H)<sup>+</sup>.

Analysis calcd. for C<sub>29</sub>H<sub>40</sub>N<sub>3</sub>O<sub>6</sub>F<sub>3</sub>·0.55H<sub>2</sub>O:

	C, 58.69;	H, 6.98;	N, 7.08;	F, 9.60.
Found:	C, 58.55;	H, 6.81;	N, 7.22;	F, 10.04.

#### Example 294

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[2-hydroxy-1-oxo-2-(trifluoromethyl)propyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethylester (isomer B) (Compound 294)



Preparative HPLC separation as described in Example 293b and work up of the fraction from the slower moving peak afforded 95 mg (24%) of the title Compound 294 (single diastereomer) as a white solid.

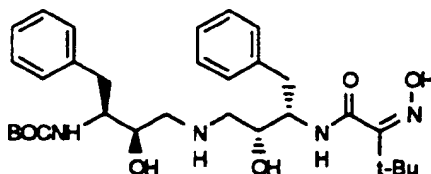
m.p. 92-95°C; [ $\alpha$ ]<sub>D</sub> = -2.5° (c 0.75, MeOH).  
Mass Spec. 584 (M+H)<sup>+</sup>.

Analysis calcd. for C<sub>29</sub>H<sub>40</sub>N<sub>3</sub>O<sub>6</sub>F<sub>3</sub>·1.23H<sub>2</sub>O:

	C, 57.50;	H, 7.06;	N, 6.94;	F, 9.41.
Found:	C, 57.70;	H, 6.70;	N, 6.74;	F, 9.67.

#### Example 295

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[2-hydroxy-3-[[2-(hydroxyimino)-3,3-dimethyl-1-oxobutyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 295)



As a solution of Compound 213c (60 mg, 91% pure, 0.10 mmol), hydroxylamine hydrochloride (22.5 mg, 0.324

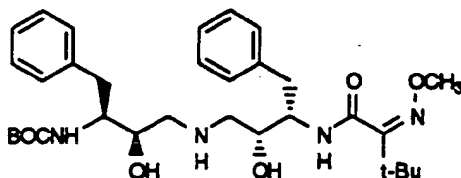
mmol) and 3 drops of pyridin in 1.0 ml absolute EtOH was stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* to provide an oily residue which was purified by chromatography on a silica gel column (11mmX20cm) eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq. NH<sub>4</sub>OH in a gradient from 98-1.8-0.2 to 92-7.2-0.8 to provide 36 mg (63% yield) of Compound 295 (white solid) as a single isomer (X-ray geometry not determined).  
 m.p. 100-104°C ("softening" at 87-100°C); [α]<sub>D</sub> = -12.4°; (c=1.1, CH<sub>3</sub>OH)  
 Mass Spec. (FAB): 571 (M+H<sup>+</sup>)

Analysis calc. for C<sub>31</sub>H<sub>46</sub>N<sub>4</sub>O<sub>8</sub> · 0.87H<sub>2</sub>O:

	C, 63.49;	H, 8.21;	N, 9.55
Found:	C, 63.47;	H, 8.02;	N, 9.57

#### Example 296

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-(methoxyimino)-3,3-dimethyl-1-oxobutyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 296)

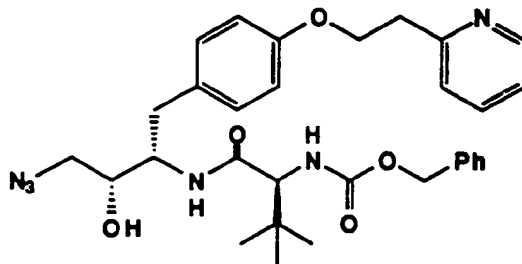


Compound 213c was reacted with methoxyamine hydrochloride by a procedure analogous to that of Example 295 to give the title Compound 296 (white solid).  
 m.p. 199-201°C ("softening" at 175-198°C); [α]<sub>D</sub> = -13.5°; (c=0.38, CH<sub>3</sub>OH)  
 Mass Spec. (FAB): 585 (M+H<sup>+</sup>)

#### Example 297

Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-[2-(2-pyridinylethoxy)phenyl]methyl]propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide (Compound 297g)

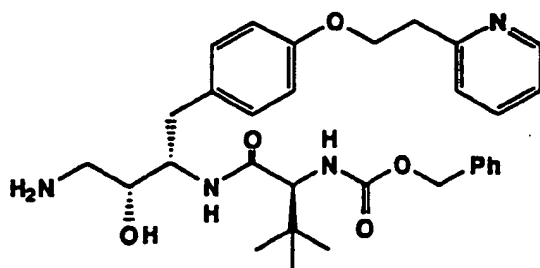
##### (a) Compound 297a



A solution of Compound 282c (410 mg, 1.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and CH<sub>3</sub>OH (5 mL) was stirred with K<sub>2</sub>CO<sub>3</sub> (3 g) at RT for 1 h, filtered, and the filtrate concentrated *in vacuo* to yield the free amine (390 mg, ca. 95% yield) as a gummy yellow residue. This material was coupled to Compound 88a (350 mg, 1.31 mmol) in 2 mL DMF, along with 251 mg (1.31 mmol) EDCI, 177 mg (1.31 mmol) HOBT and 170 μl (1.55 mmol) N-methylmorpholine, using a procedure analogous to that described in Example 93f, to give Compound 297a (421

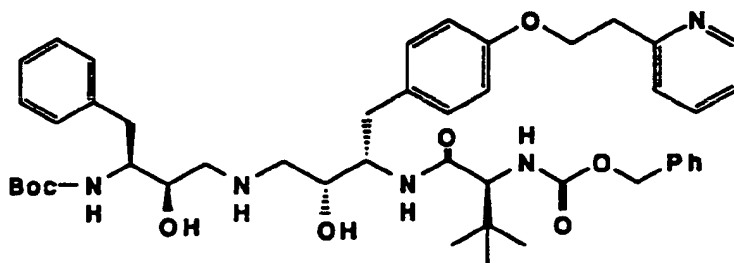
mg, 61%).

(b) Compound 297b



Compound 297a (420 mg, 0.729 mmol) was treated with triphenylphosphine (210.5 mg, 0.802 mmol) in THF (4.5 mL) and water (20  $\mu$ L), using a procedure analogous to that of Example 282e to afford Compound 297b (318 mg, 79%) as a gummy residue.

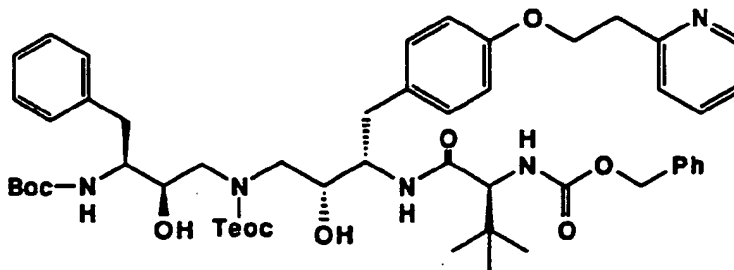
(c) Compound 297c



Compound 297b (314 mg, 0.571 mmol) was taken in DMF (1.0 mL) and heated with the Compound 1b(i) (150.2 mg, 0.571 mmol) using a procedure analogous to that of Example 282f to afford Compound 297c (296 mg, 63% yield) as a yellow residue.

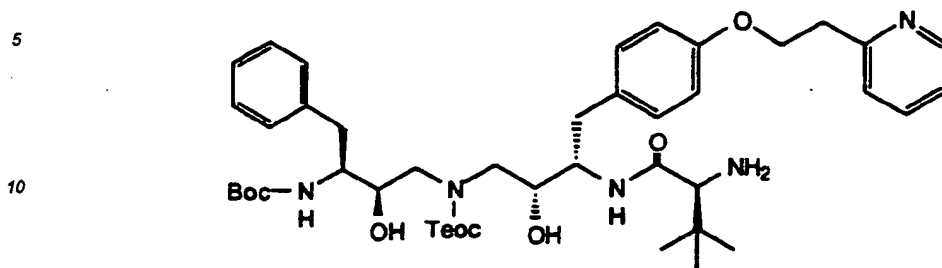
TLC( $\text{SiO}_2$ )  $R_f$  = 0.28 (9:1:0.1  $\text{CH}_2\text{Cl}_2$ : $\text{CH}_3\text{OH}$ : aq.  $\text{NH}_4\text{OH}$ -Rydon)

(d) Compound 297d



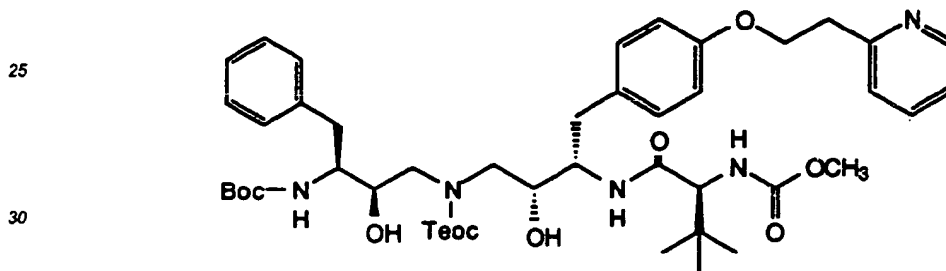
To a solution of Compound 297c (291 mg, 0.358 mmol) in DMF (1 mL), was added  $i\text{-Pr}_2\text{NEt}$  (130  $\mu$ L, 0.752 mmol) and 2-trimethylsilylethylchloroformate (72 mg, 0.394 mmol) at 0°C, and the mixture stirred for 2.5 h. The reaction mixture was diluted with EtOAc and poured into a 1:1 mixture of saturated  $\text{NaHCO}_3$ : $\text{H}_2\text{O}$ . The organic layer was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated under vacuum to yield a gummy residue which was purified by silica gel chromatography, eluting with  $\text{CH}_3\text{OH}$  (3% to 8%)- $\text{CH}_2\text{Cl}_2$  to afford Compound 297d (305 mg, 89% yield) as a foamy white residue.

TLC( $\text{SiO}_2$ )  $R_f$  = 0.53 (8%  $\text{CH}_3\text{OH}$ - $\text{CH}_2\text{Cl}_2$ -Rydon)

( ) Compound 297e

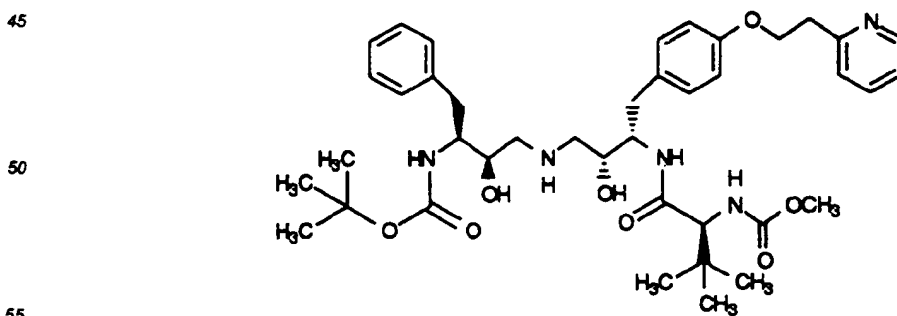
15 Compound 297d (303 mg, 0.316 mmol) in EtOH (4 mL) was treated with 20% Pd(OH)<sub>2</sub>/C (104 mg) under a H<sub>2</sub> atmosphere for 18 h. The catalyst was filtered and the filtrate concentrated. The crude product was purified by silica gel chromatography, eluting with CH<sub>3</sub>OH (2.5% to 7.5%)-CH<sub>2</sub>Cl<sub>2</sub>, to afford Compound 297e (185 mg, 71% yield) as a yellow solid.  
TLC(SiO<sub>2</sub>) R<sub>f</sub> = 0.27 (8% CH<sub>3</sub>OH-CH<sub>2</sub>Cl<sub>2</sub>-Rydon)

20

(f) Compound 297f

35 To a solution of Compound 297e (85 mg, 0.103 mmol) in p-dioxane (0.8 mL) was added a 1:1 mixture of saturated NaHCO<sub>3</sub>:H<sub>2</sub>O (400  $\mu$ L), followed by methyl chloroformate (0.114 mmol, 8.7  $\mu$ L) and the mixture stirred at RT for 30 min. Additional methyl chloroformate was added (3.3 eq.; 27  $\mu$ L total in small portions), and stirred at RT for a total of 3.5 h. The reaction mixture was diluted with EtOAc and washed with saturated NaHCO<sub>3</sub> and brine and the organic layer was dried and concentrated *in vacuo* to yield crude Compound 297f (86 mg, 94% yield) as a gray solid.

40 TLC(SiO<sub>2</sub>) R<sub>f</sub> = 0.25 (5% CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>-PMA)

(g) Compound 297g

To a solution of Compound 297f (86 mg, 0.097 mmol) in dry THF (1 mL) was added n-Bu<sub>4</sub>NF (76.6 mg, 0.293 mmol) and the reaction mixture heated at 45°C for 4 h. The mixture was concentrated *in vacuo* and chromatographed on silica gel, eluting with CH<sub>3</sub>OH (2.5% to 6.5%)-CH<sub>2</sub>Cl<sub>2</sub> with aq. NH<sub>4</sub>OH (0.25% to 0.6%) to af-

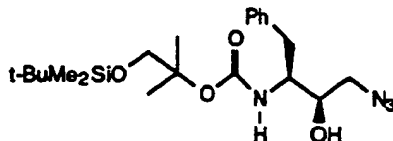


Found: C, 64.31; H, 7.49; N, 9.55

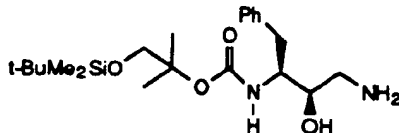
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-2-Hydroxy-3-[[2-hydroxy-3-[(2-hydroxy-1,1-dimethylethoxy)carbonyl]amino]-4-phenylbutyl]amino]-1-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 298e)

N[C@@H](c1ccccc1)[C@H](O)CN=[N+]=[N-].[Cl-]

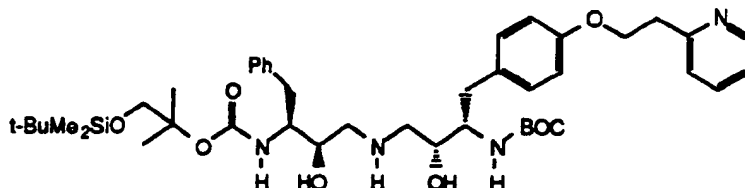
**(b) Compound 298b**



**(c) Compound 298c**

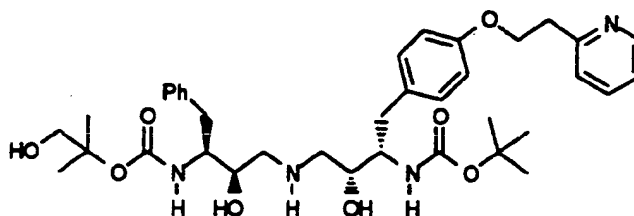


285

(d) Compound 298d

A solution of 184 mg (0.45 mmol) of Compound 298c and 165 mg (0.43 mmol) of Compound 282a in 1 ml of dry DMF was heated at 100°C for 7 h. After removal of solvent, the residue was purified by flash chromatography on a 35 cc column of silica gel. Elution with  $\text{CHCl}_3:\text{MeOH}:\text{NH}_4\text{OH}$  (95:5:0.5) afforded 113 mg (33 %) of Compound 298d as a solid foam.

TLC( $\text{SiO}_2$ )  $R_f = 0.32$  ( $\text{CHCl}_3:\text{MeOH}:\text{NH}_4\text{OH}$  90:10:1)

(e) Compound 298e

A solution of 110 mg (0.14 mmol) of Compound 298d in 1 ml  $\text{HOAc}:\text{H}_2\text{O}:\text{THF}$  (3:1:1) was stirred at RT for 48 h. After removal of solvent, the residue was purified by flash chromatography on a 35 cc column of silica gel. Elution with  $\text{CHCl}_3:\text{MeOH}:\text{NH}_4\text{OH}$  (95:5:0.5) afforded 67 mg of material which was further purified by trituration with  $\text{Et}_2\text{O}$  to afford 60 mg (63%) of the title Compound 298e as a white powder; m.p. 125-126°C;  $[\alpha]_D = -3.4^\circ$  (c 0.82, MeOH)

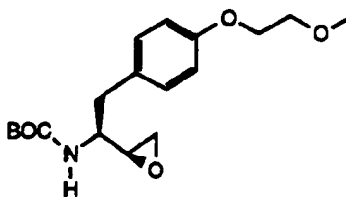
Mass Spec:  $(\text{M}+\text{H})^+ 681^+$

Analysis Calc. for  $\text{C}_{37}\text{H}_{52}\text{N}_4\text{O}_8 \cdot 0.87 \text{ H}_2\text{O}$ :

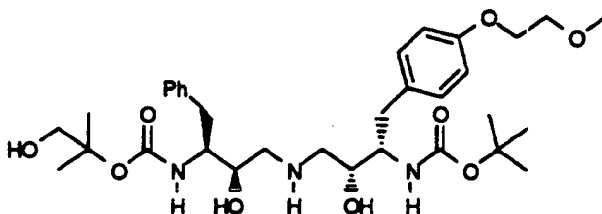
	C, 63.81;	H, 7.78;	N, 8.04.
Found:	C, 63.88;	H, 7.53;	N, 8.04.

## Example 299

Preparation of [1S-[1R\*, 2S\*(2S\*,3R\*)]-3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-methoxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1-(hydroxymethyl)-1-methylethyl ester (Compound 299b)

(a) Compound 299a

To a solution of 200 mg (0.72 mmol) of Compound 175c, 113  $\mu$ l (1.44 mmol) of 2-methoxyethanol and 377 mg (1.44 mmol) of  $\text{PPh}_3$  in 3 ml of dry THF at RT, was added 226  $\mu$ l (1.44 mmol) of DEAD. Stirring was continued overnight. After removal of solvent, flash chromatography of the oil residue on silica gel (25 % EtOAc-hexane) afforded 198 mg (81%) of Compound 299a as a white solid.

(b) Compound 299b

Compounds 298c and 299a were reacted by a two-step procedure analogous to that used for the conversion of Compound 298c to Compound 298e to give the title Compound 299b (white solid).  
m.p. 128-130°C;  $[\alpha]_D = -4.0^\circ$  (c 0.89, MeOH)  
Mass Spec.:  $(\text{M}+\text{H})^+ 634^+$

Analysis Calc. for $\text{C}_{33}\text{H}_{51}\text{N}_3\text{O}_9 \cdot 0.42 \text{ H}_2\text{O}$ :			
	C, 61.81;	H, 8.15;	N, 6.55.
Found:	C, 61.88;	H, 8.21;	N, 6.48.

## Example 300

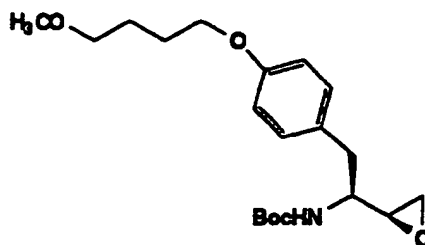
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-[4-(4-methoxybutoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 300d)

(a) Compound 300a

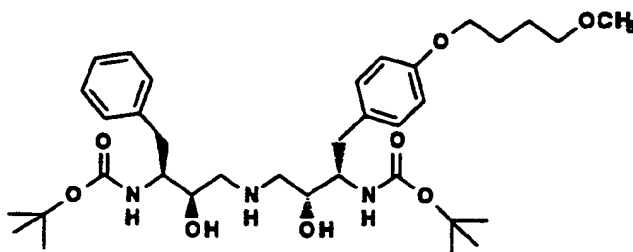
4-Penten-1-ol (1.80 ml; 17.5 mmol) was added dropwise over 1 h to a suspension of pentane washed NaH (770 mg 60% in oil; 19.2 mmol) in 35 ml of DMF at 0°C. After stirring at 0°C for 30 min, methyl iodide (1.40 ml; 21.8 mmol) was added dropwise over 15 min and the reaction mixture was allowed to warm to RT. After stirring 18 h at RT, the excess methyl iodide was pumped off (dry ice trap).  $\text{H}_2\text{O}$  was then added and the mixture was extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with  $\text{H}_2\text{O}$  and brine, dried ( $\text{MgSO}_4$ ) and most of the  $\text{Et}_2\text{O}$  was removed at atmospheric pressure to give a concentrated solution of Compound 300a in  $\text{Et}_2\text{O}$  which was used without further purification.

(b) Compound 300b

Compound 300a was converted to Compound 300b by a procedure analogous to that of Example 277b.

(c) Compound 300c

Compounds 175c and 300b were reacted by a procedure analogous to that of Example 282a to give Compound 300c.

(d) Compound 300d

Compounds 300c and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 300d (white solid).

m.p. 118-125°C;  $[\alpha]_D^{25} = +1.4^\circ$  (0.59, MeOH).

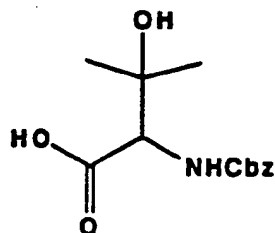
Mass Spec. FAB: M+H= 646.

Analysis calc. for  $C_{35}H_{55}N_3O_8 \cdot 1.39 H_2O$ :

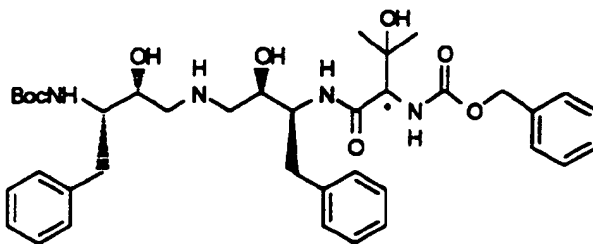
	C, 62.67;	H, 8.68;	N, 6.26;
Found:	C, 62.50;	H, 8.43;	N, 6.43.

Example 301

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-hydroxy-2-methylpropyl]carbamic acid, phenylmethyl ester, isomer A (Compound 301b)

(a) Compound 301a

Compound 239b was converted to Compound 301a by a procedure analogous to that of Example 205a.

(b) Compound 301b

Compounds 301a and 54 were reacted by a procedure analogous to that of Example 55 (DMF only used) to give the Compound 301b along with its diastereomer (at -) Compound 302. Flash chromatography (silica gel, 5 by 10.5 cm), eluting with a step-wise gradient of MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub> (5:0.5:94.5 to 8:0.8:91.2) followed by trituration of the faster moving isomer with hot Et<sub>2</sub>O gave the title Compound 301b (53 mg, 17% yield) as a colorless solid.

$R_f = 0.39$  (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>); m.p. 164-166°C;  $[\alpha]_D = +7.89^\circ$  (c 0.34, MeOH).

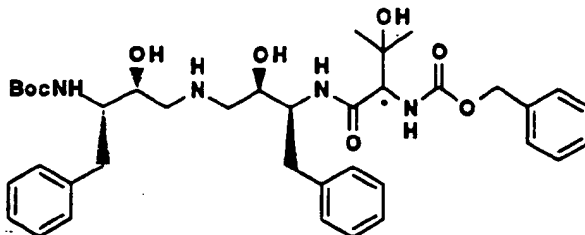
Anal. Calc. for C<sub>38</sub>H<sub>52</sub>N<sub>4</sub>O<sub>8</sub> • 0.58 H<sub>2</sub>O

C, 64.90; H, 7.62; N, 7.97

Found: C, 64.97; H, 7.55; N, 7.90

Example 302

Preparation of [1S-[1R\*.2S\*(2S\*.3R\*)]]-[1-[[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-hydroxy-2-methylpropyl]carbamic acid, phenylmethyl ester, isomer B (Compound 302)



Flash chromatography of the diastereomeric mixture described in Example 301 followed by trituration of

the slow r moving isomer with hot Et<sub>2</sub>O and with h t EtOAc gave Compound 302 (48 mg, 15% yield) as a colorless solid.  $R_f = 0.33$  (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>); m.p. 185-189°C;  $[\alpha]_D = -17.3^\circ$  (c 0.15, MeOH).

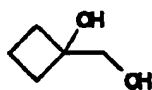
Anal. Calc. for C<sub>38</sub>H<sub>52</sub>N<sub>4</sub>O<sub>8</sub> · 0.26 H<sub>2</sub>O

	C, 65.44;	H, 7.59;	N, 8.03
Found:	C, 65.54;	H, 7.53;	N, 7.93.

### Example 303

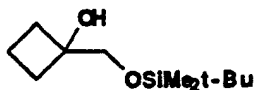
Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[[carbamic acid], 1-(hydroxymethyl)cyclobutyl 1,1-dimethylethyl ester (Compound 303e)

#### (a) Compound 303a



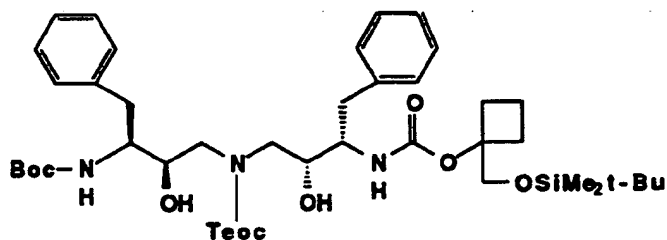
Compound 303a was prepared as described in *J. Am. Chem. Soc.*, 71, 3925 (1949).

#### (b) Compound 303b

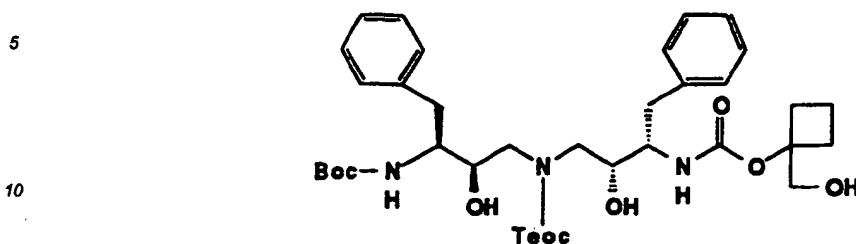


Compound 303a was converted to Compound 303b by a procedure analogous to that of Example 277c.

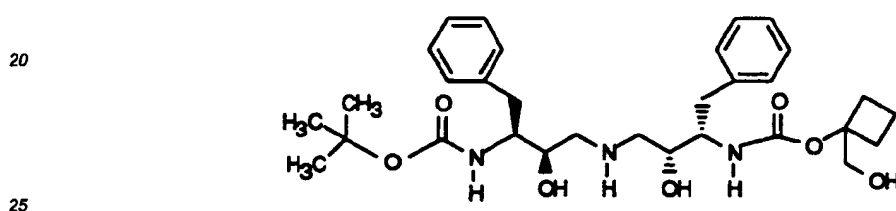
#### (c) Compound 303c



Compounds 303b and 48 were converted to Compound 303c by a two-step procedure analogous to that used for the conversion of Compound 149c to Compound 149e (DMF was used in the coupling of the p-nitrophenylcarbonate of Compound 303b with Compound 48).

(d) Compound 303d

Compound 303c was converted to Compound 303d by a procedure analogous to that of Example 162.

(e) Compound 303e

Compound 303d was converted to the title Compound 303e (light-brown solid) by a three-step procedure analogous to that used for the conversion of Compound 289a to Compound 289d.

m.p. 139-145°C;  $[\alpha]_D^{25} = -5.1^\circ$  (c 0.2, CH<sub>3</sub>OH).

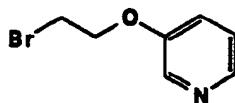
Mass Spec. (FAB) (M + H)<sup>+</sup> = 572

Analysis calc. for C<sub>31</sub>H<sub>45</sub>N<sub>3</sub>O<sub>7</sub>·2.05H<sub>2</sub>O:

	C, 61.17;	H, 8.13;	N, 6.90;
Found:	C, 60.95;	H, 7.70;	N, 7.12.

Example 304

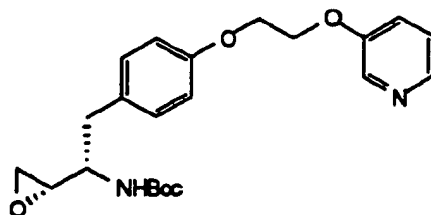
Preparation of [1S-[1R\*,2S\* (2S\*, 3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(3-pyridinyloxy)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 304c)

(a) Compound 304a

To a 0°C suspension of 3-hydroxypyridine (1.00 g; 10.5 mmol), Ph<sub>3</sub>P (7.08 g; 27.0 mmol), and bromoethanol (1.91 mL; 27.0 mmol) in anhydrous THF (30 mL) was added dropwise DEAD (4.25 mL; 27.0 mmol) over 15 min. The resulting yellow solution was allowed to warm to RT and stirred for 36 h. Volatiles were removed *in vacuo* to give a yellow-brown residue, which was dissolved in EtOAc and Et<sub>2</sub>O (1:1). This solution was extracted with aqueous 1 N HCl and the aqueous extracts basified at 0°C with excess 1 M aq. NaOH. Extraction with EtOAc followed by drying (MgSO<sub>4</sub>) and evaporation *in vacuo* gave an oil which was purified on silica gel (150 mL) using a stepwise gradient from 3:1 to 1:2 hexanes:EtOAc to afford Compound 304a (1.27 g; 60%) as a

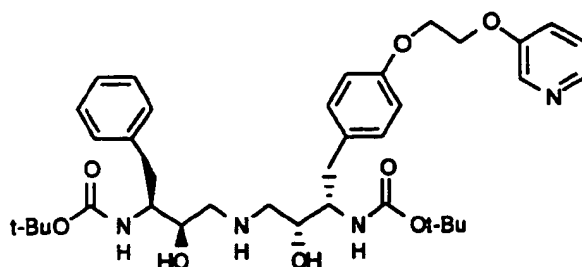
yellow il.

(b) Compound 304b



To a 0°C suspension of NaH (0.032 g of a 60% suspension in oil) in anhydrous DMF (1.0 mL) was added dropwise a solution of Compound 175c (0.200 g; 0.716 mmol) in DMF (1.0 mL). The solution was stirred at RT for 1 h, then recooled to 0°C. A solution of Compound 304a (0.167 g; 0.827 mmol), *n*-Bu<sub>4</sub>NI (0.015 g; 0.039 mmol) and 15-crown-S (0.159 mL; 0.80 mmol) in DMF (1.0 mL) was added dropwise. The reaction was stirred at RT for 24 h. Volatiles were removed *in vacuo*, and the residue was partitioned between H<sub>2</sub>O and EtOAc. The organic extracts were washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an oil, which was purified on silica gel (100 mL) using a gradient from 3:1 to 1:3 hexane:EtOAc as eluent to give Compound 304b (0.168 g; 59%) as a white solid.

(c) Compound 304c



Compound 304b (0.160 g; 0.400 mmol) was reacted with Compound 16b (0.112 g; 0.400 mmol) in DMF at 100°C for 5 h. Volatiles were removed *in vacuo* and the residue was chromatographed on silica gel (100 mL) using as eluent a stepwise gradient from 99:1:0.1 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH to afford a white solid (0.125 g, 46%). This material was further purified by preparative HPLC on a C-18 column (6μm- 30 X 300 cm; using a stepwise gradient from 50:50 to 75:25 A:B; A=90:10:0.05 MeOH:H<sub>2</sub>O:TFA; B=90:10:0.05 H<sub>2</sub>O:MeOH:TFA) followed by basification with saturated aq. NaHCO<sub>3</sub>, extraction with EtOAc, concentration and lyophilization from dioxane-H<sub>2</sub>O to afford the title Compound 304c (0.091 g; 34%) as a white solid.

m.p. = 127°-130°C ; [α]<sub>D</sub> = -3.5° (c = 0.34; MeOH)

Mass Spec. (CI): (M + H)<sup>+</sup> = 681;

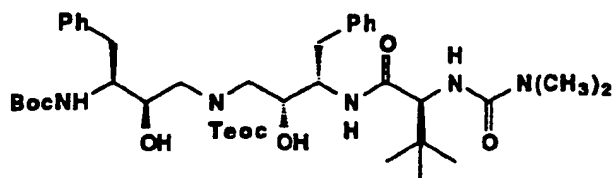
Analysis calc. for C<sub>37</sub>H<sub>52</sub>N<sub>4</sub>O<sub>8</sub>·0.80 H<sub>2</sub>O:

	C, 63.92;	H, 7.77;	N, 8.06
Found:	C, 64.24;	H, 7.72;	N, 7.74

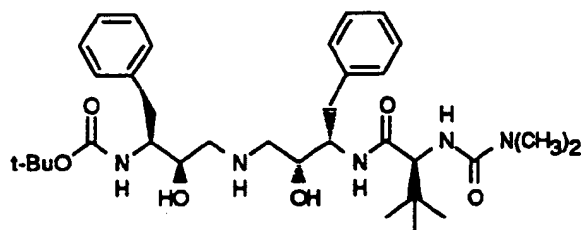
Example 305

Preparation of [1R\*,2S\* (2S\*,3R\*)]-N-[3-[[[(1,1-Dimethyl th xy)carbonyl]amin ]-2-hydroxy-4-ph nylbu-tyl]amin ]-2-hydroxy-1-(ph nylm thyl)propyl]-N<sup>2</sup>[(dimethylamino)carbonyl]-3-m thyl-L-valinamid (Com-pound 305b)



(a) Compound 305a

To a 0°C solution of Compound 263b (0.271 g; 0.387 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was added dimethyl carbamyl chloride (0.050 g; 0.464 mmol) dropwise, followed by dry Et<sub>3</sub>N (0.129 mL, 0.930 mmol). The reaction was allowed to warm to RT and stirred for 24 h. Additional dimethyl carbamyl chloride (0.040 g; 0.372 mmol) and Et<sub>3</sub>N (0.100 mL; 0.718 mmol) were added and the reaction was stirred for another 24 h. Aqueous NaHCO<sub>3</sub> (10 mL of a 50% saturated solution) was added and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel (150 mL) with a stepwise gradient from 2:1 to 1:4 hexanes:EtOAc to afford Compound 305a (0.193 g; 65%) as a white foam.

(b) Compound 305b

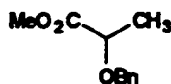
Compound 305a was converted to the title Compound 305b (white solid) by a procedure analogous to that of Example 21.

m.p. = 146°-150°C (dec.); [ $\alpha$ ]<sub>D</sub> = -12.5° (c = 0.20; MeOH).

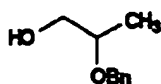
Mass Spec. (FAB): (M + H)<sup>+</sup> = 628.

Example 306

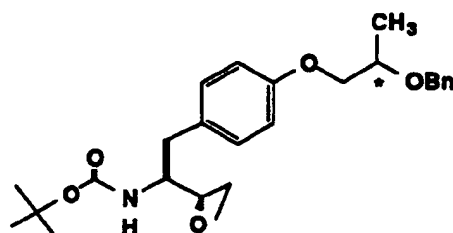
Preparation of [1S-[1R\*, 2S\* (2S\*, 3R\*)]-3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxypropoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 306e)

(a) Compound 306a

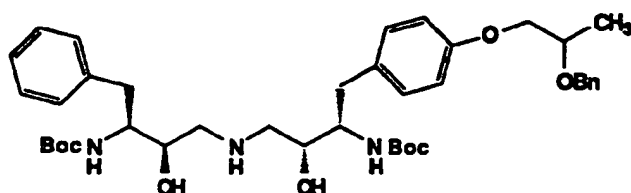
To a 0°C suspension of THF-washed NaH (1.0 g of a 60% suspension in oil) was added dropwise a solution of methyl lactate (2.10 mL; 22.0 mmol) in 10 mL of dry THF over 15 min. The reaction mixture was allowed to warm to 20°C and stirred for 30 min. The solution was cooled to 0°C and benzyl bromide (2.97 mL; 25 mmol) in 5 mL of dry THF was added, followed by Bu<sub>4</sub>NI (0.092 g; 0.25 mmol). The reaction solution was allowed to warm to RT and stirred for 24 h. The reaction mixture was partitioned between H<sub>2</sub>O and EtOAc and the combined organic extracts were washed with H<sub>2</sub>O and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Volatiles were removed *in vacuo* to give an oil, which was purified on silica gel using a gradient from hexane to 10% EtOAc/hexane to afford Compound 306a (2.46 g; 57%) as a clear, colorless oil.

(b) Compound 306b

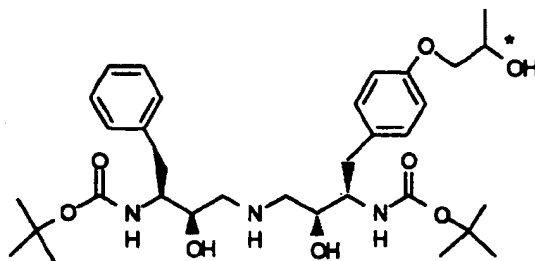
Compound 306a was converted to Compound 306b by a procedure analogous to that of Example 281a (reaction was run at 0°C to RT).

(c) Compound 306c

Compounds 306b and 175c were reacted by a procedure analogous to that of Example 282a to give Compound 306c.

(d) Compound 306d

Compounds 306c and 16b were reacted by a procedure analogous to that of Example 226b to give the Compound 306d.

(e) Compound 306e

To a suspension of 10% Pd/C (60 mg) in MeOH (2.5 mL) was added Compound 306d (64 mg; 0.09 mmol) followed by aq. HCl (900 µL of a 0.1N solution) and the reaction was placed under an atmosphere of H<sub>2</sub>. After 1 h, the reaction mixture was neutralized with 900 µL of 0.1N NaOH, filtered through a Celite plug and concentrated *in vacuo*. The crude product was purified on silica gel using a stepwise gradient from 98:2:0.2 to 92:8:0.8 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH to afford Compound 306e (35 mg; 65%) as a white solid. m.p. = 145-147°C

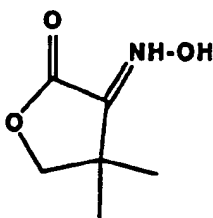
Mass Spec. (CI): (M+H) = 618

Analysis calc. for  $C_{33}H_{51}N_3O_8 \cdot 0.94 H_2O$ 

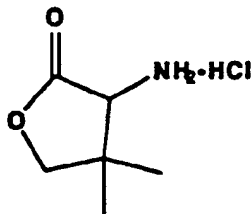
C, 62.44;	H, 8.40;	N, 6.62
C, 62.89;	H, 8.17;	N, 6.17

**Example 307**

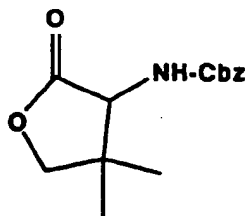
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenyl-butyl]amino]-2-hydroxy-1-(phenylmethyl)-propyl]amino]carbonyl]-3-[[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2,2-dimethylpropyl]carbamic acid, phenylmethyl ester, isomer A (Compound 307e)

**(a) Compound 307a**

To a solution of dihydro-4,4-dimethyl-2,3-furandione (0.5 g, 3.76 mmol) in HOAc (20 mL) was added KOAc (1.0 g, 0.01 mol) and then  $H_2NOH \cdot HCl$  (0.70 g, 0.01 mol). After 1.2 h, the reaction mixture was partitioned between EtOAc and  $H_2O$ , and the aqueous layer extracted with EtOAc. The combined organic extracts were dried ( $Na_2SO_4$ ) and evaporated *in vacuo* to give Compound 307a (1.28 g, 89% yield) as a colorless solid.

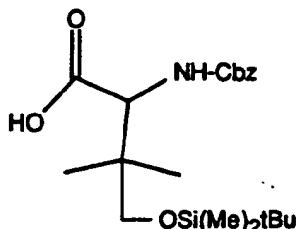
**(b) Compound 307b**

A solution of Compound 307a (710 mg, 4.96 mmol) in EtOH (3 mL) was added to a suspension of 180 mg of 5% Pd/C in EtOH (10 mL) and 2N HCl (5 mL) and the mixture stirred under a  $H_2$  atmosphere. After 4 h, the reaction mixture was filtered through a Nylon plug and the filtrate evaporated *in vacuo* to give Compound 307b (826 mg,  $\leq 100\%$  crude yield) as an oily solid after co-evaporation from MeOH.

**(c) Compound 307c**

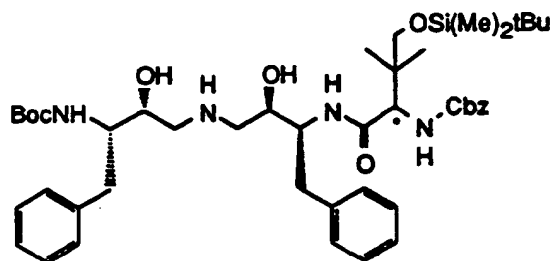
To a 0°C solution of Compound 307b ( $\leq 0.82$  g,  $\leq 3.47$  mmol) in aqueous 0.83 M  $\text{NaHCO}_3$  (10 mL) was added Cbz-Cl (0.50 mL, 3.26 mmol). After 15 min, the reaction mixture was brought to RT for 3 h and a second portion of Cbz-Cl (0.10 mL, 0.65 mmol) was added. After a total of 5 h, the reaction mixture was filtered, washing the solid with  $\text{H}_2\text{O}$  and hexanes. The solid residue was purified by flash chromatography (silica gel, 5 by 10 cm), eluting with 2% EtOAc: $\text{CH}_2\text{Cl}_2$  to give Compound 307c (567 mg, 61% yield for the 2 steps) as a colorless solid.

(d) Compound 307d



To a solution of Compound 307c (500 mg, 1.90 mmol) in THF (15 mL) was added an aqueous solution of LiOH (80 mg, 1.91 mmol). After 1.45 h the volatiles were evaporated *in vacuo* to give the lithium salt (826 mg,  $\leq 100\%$  crude yield) as an oily solid after co-evaporation with dry THF and with dry DMF. The crude residue ( $\leq 1.90$  mmol) was dissolved in DMF (7 mL) and imidazole (320 mg, 4.7 mmol) and then t-butyldimethylsilyl chloride (630 mg, 4.18 mmol) was added. After stirring 23 h, MeOH (8 mL) was added and the mixture was stirred for 21 h, then stored at -80°C. After warming, the volatiles were removed *in vacuo* and the oily residue was partitioned between EtOAc and saturated  $\text{NH}_4\text{Cl}$ . The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give an oil which was purified by flash chromatography (silica gel, 5 by 9 cm), eluting with EtOAc: $\text{CH}_2\text{Cl}_2$  (6, 7 and then 20% EtOAc containing 1% AcOH) to give Compound 307d (450 mg, 60% yield for the 2 steps) as an oily solid after co-evaporation with heptane.

(e) Compound 307e



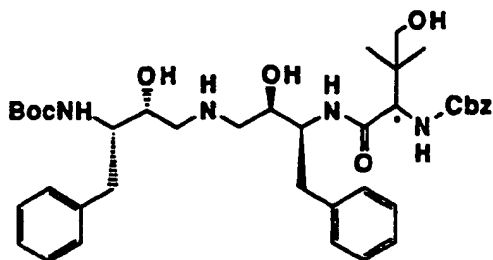
(single isomer at •)

To a solution of Compound 307d (345 mg, 0.873 mmol) and Compound 54 (410 mg, 0.925 mmol) in DMF (6 mL) at 0°C under argon was added HOBt (190 mg, 1.41 mmol), EDCI (170 mg, 0.887 mmol), and then N-methylmorpholine (0.1 mL, 0.91 mmol). The mixture was allowed to come to RT and stirred for 20 h. The reaction mixture was partitioned between EtOAc and saturated  $\text{NaHCO}_3$ , and the combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and evaporated *in vacuo* to leave an oil. The residue was purified by flash chromatography (silica gel, 5 by 10 cm), eluting with a gradient of MeOH: $\text{NH}_4\text{OH}$ : $\text{CH}_2\text{Cl}_2$  (2:0.2:97.8, 3:0.3:96.7, 3.5:0.35:96.15, 4:0.4:95.6, 4.5:0.45:95.05, 5:0.5:94.5, and then 6:0.6:93.4) to give the title Compound 307e (170 mg, 47%) as a colorless glass (single isomer).  $R_f$  ( $\text{SiO}_2$ ) = 0.45 (10:1:89 MeOH: $\text{NH}_4\text{OH}$ : $\text{CH}_2\text{Cl}_2$ ); Compound 309a was also isolated.

Exempl 308

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[3-[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-(hydroxymethyl)-2-methylpropyl] carbamic

acid, phenylmethyl ester, isomer A (Compound 308)



(single isomer at •)

A solution of Compound 307e (162 mg, 0.197 mmol) in AcOH:THF:H<sub>2</sub>O (5 mL, 3:1:1) was stirred at RT for 59.5 h and the volatiles were removed *in vacuo*. The oily residue was co-evaporated once with heptane and then twice with heptane/CH<sub>2</sub>Cl<sub>2</sub> to leave an oily solid residue. The residue was purified by flash chromatography (silica gel, 2.5 by 18 cm), eluting with MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub> (6:0.6:93.4 and then 7:0.7:92.3) to give the title Compound 308 (98 mg, 70%) as a colorless solid.

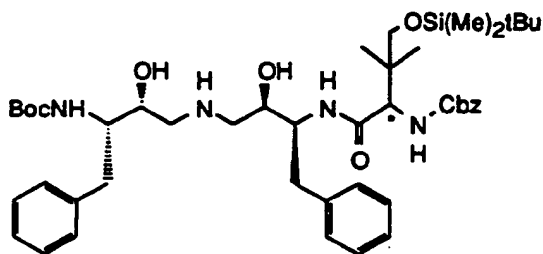
$R_f$  (SiO<sub>2</sub>) = 0.29 (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>); m.p. 68-70°C;  $[\alpha]_D = -19.8^\circ$  (c 0.19, MeOH). (FAB): 707 (M+H).

Analysis Calc. for C <sub>39</sub> H <sub>54</sub> N <sub>4</sub> O <sub>8</sub> · 0.46 H <sub>2</sub> O:			
	C, 65.51;	H, 7.74;	N, 7.83
Found:	C, 65.45;	H, 7.62;	N, 7.89

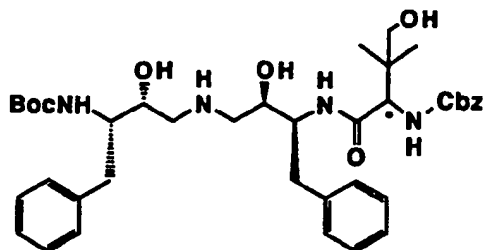
### Example 309

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-(hydroxymethyl)-2-methylpropyl] carbamic acid, phenylmethyl ester, isomer B (Compound 309b)

#### (a) Compound 309a



Flash chromatography of the reaction mixture from Example 307e gave Compound 309a, the diastereomer at • of Compound 307e.  $R_f$  (SiO<sub>2</sub>) = 0.43 (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>).

(b) Comp und 309b

Compound 309a was converted to the title Compound 309b (colorless solid) by a procedure analogous to that of Example 308.

$R_f$  (SiO<sub>2</sub>) = 0.35 (10:1:89 MeOH:NH<sub>4</sub>OH:CH<sub>2</sub>Cl<sub>2</sub>); m.p. 72-76°C;  $[\alpha]_D = -9.72^\circ$  (c 0.26, AcOH).

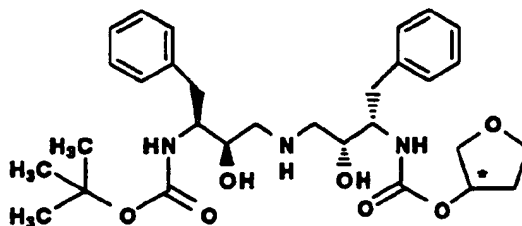
Mass Spec.: (FAB): 707 (M+H).

Anal. Calc. for C<sub>39</sub>H<sub>54</sub>N<sub>4</sub>O<sub>8</sub> · 0.47 H<sub>2</sub>O:

	C, 65.49;	H, 7.74;	N, 7.83
Found:	C, 65.50;	H, 7.64;	N, 7.82

Example 310

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)3,1-propanediyl]]bis[carbamic acid], 3-tetrahydrofuranyl 1,1-dimethylethyl ester (Compound 310)



(1:1 mixture of isomers at \*)

3-Hydroxytetrahydrofuran and Compound 48 were reacted by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used in the coupling of the p-nitrophenylcarbonate with Compound 48) to give the title Compound 310 (white solid).

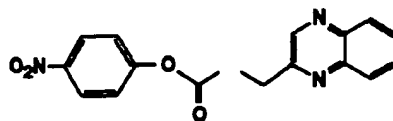
m.p. 200-203°C;  $[\alpha]_D = -11^\circ$  (c = 0.2, CH<sub>3</sub>OH)

Analysis calc. for C<sub>30</sub>H<sub>43</sub>N<sub>3</sub>O<sub>7</sub> · 0.26 H<sub>2</sub>O:

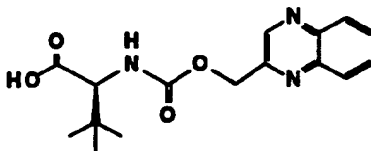
	C, 63.84;	H, 8.13;	N, 7.44
Found:	C, 63.89;	H, 7.70;	N, 7.39

Example 311

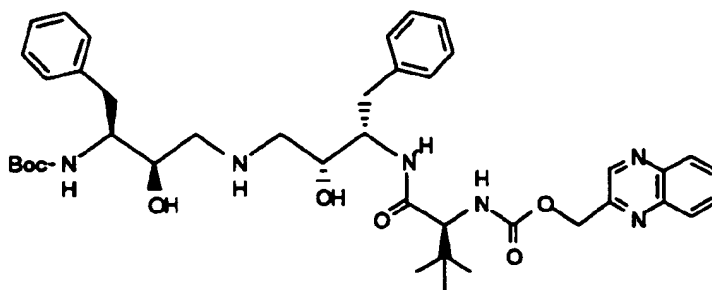
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[3-[[[(1,1-dimethylthoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]aminocarbonyl]propyl]carbamic acid, (2-quinoxaliny)methyl ester (Compound 311c)

(a) Compound 311a

A solution of 2-hydroxymethyl quinoxaline (Lindquist, *J. Chem. Soc.*, 2052-8 (1956)) (160.2 mg, 1.0 mmol) in 4 ml of  $\text{CH}_2\text{Cl}_2$  was cooled to  $0^\circ\text{C}$  and pyridine (87 mg, 1.1 mmol) was added followed by the addition of p-nitrophenylchloroformate (222 mg, 1.1 mmol) in 2 ml of  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred at  $0^\circ\text{C}$  for 3 h and slowly warmed to RT and stirred overnight. The reaction was diluted with EtOAc and washed with  $\text{H}_2\text{O}$  and brine. After drying over  $\text{Na}_2\text{SO}_4$  the solvents were evaporated yielding the crude product as a yellow solid. The product was purified by chromatography on CC-7 (buffered silica, pH 6.8) eluting with EtOAc/hexane (1:1) to afford 304 mg (93%) of Compound 311a as a colorless solid.

(b) Compound 311b

L-*tert*-Leucine (112 mg, 0.85 mmol) was dissolved in 0.85 ml of 1 N NaOH and a solution of Compound 311a (275 mg, 0.85 mmol) in 1.5 ml of dioxane was added at RT followed by the addition of  $\text{Et}_3\text{N}$  (91 mg, 1.55 mmol). The reaction was stirred overnight, diluted with 5%  $\text{KHSO}_4$  and extracted with EtOAc. The combined EtOAc extracts were washed with  $\text{H}_2\text{O}$  and brine and the solvents evaporated yielding the crude product as a pale yellow solid. The crude material was purified on a silica column eluting with 5-10% MeOH/ $\text{CH}_2\text{Cl}_2$  to afford 198 mg (73%) of the Compound 311b as a colorless solid.

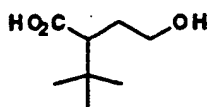
(c) Compound 311c

A mixture of Compound 54 (273 mg, 0.6 mmol), Compound 311b (195 mg, 0.6 mmol) and HOBT (94 mg, 0.6 mmol) was dissolved in 2 ml of dry DMF and the mixture cooled to  $0^\circ\text{C}$ . EDCI (118 mg, 0.6 mmol) was added and the mixture stirred at  $0^\circ\text{C}$  for 3 h and then slowly allowed to warm to RT and stir overnight. The reaction was diluted with EtOAc and washed with 5%  $\text{KHSO}_4$ ,  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$  and brine. The solvents were evaporated and the crude residue was purified on a silica column eluting with 3-5% MeOH/ $\text{CH}_2\text{Cl}_2$  + 0.1%  $\text{NH}_4\text{OH}$  to afford 198 mg (44%) of the title Compound 311c as a colorless solid.  
m.p.  $178-184^\circ\text{C}$  (dec);  $[\alpha]_D = -14.5^\circ$  ( $c = 0.25$ , MeOH).  
Mass Spec. (FAB):  $(\text{M}+\text{H})^+ = 743^+$

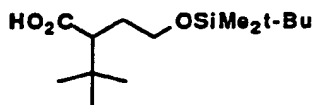
Analysis Calcd. for $C_{41}H_{64}N_6O_7 \cdot 0.45 H_2O$ :			
	C, 65.58	H, 7.37	N, 11.1
Found:	C, 65.62	H, 7.41;	N, 11.15

**Example 312**

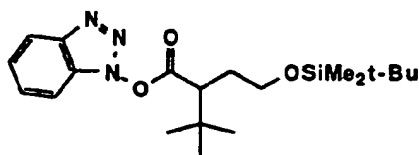
Preparation of [1S-[1R\*, 2S\* (2S\*, 3R\*)]]-[3-[[2-(1,1-Dimethylethyl)-4-hydroxy-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 312d)

**(a) Compound 312a**

Compound 312a was prepared as described in *Chem. Ber.* 123, 2167-2172 (1990).

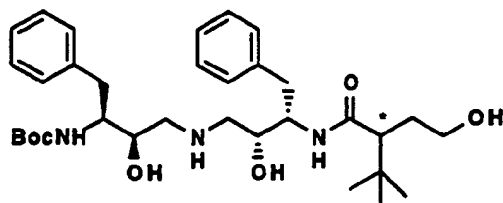
**(b) Compound 312b**

Compound 312a was converted to Compound 312b by a procedure analogous to that of Example 291b.

**(c) Compound 312c**

To a 5°C mixture of Compound 312b (250 mg, 0.91 mmol) and HOBt hydrate (149 mg, 1.1 mmol) in  $CH_2Cl_2$  (1 mL) and DMF (0.5 mL) was added EDCI hydrochloride (192 mg, 1.0 mmol). The mixture was allowed to warm to RT and was stirred overnight. The mixture was concentrated to remove most of the DMF and the residue was partitioned between EtOAc and sat'd. aq.  $NaHCO_3$ . The combined organic extracts were washed with  $H_2O$  and brine, dried ( $Na_2SO_4$ ) and concentrated to afford a crude residue which was purified by column chromatography on silica gel eluting with EtOAc-hexane (80-20) to afford 324 mg (91% yield) of Compound 312c as a white solid.



(d) Compound 312d

A mixture of Compound 54 (365 mg, 0.82 mmol) and Compound 312c (269 mg, 0.69 mmol) in 1.2 mL dry DMF was heated at 75-80°C for 4 hr. The mixture was cooled to RT and concentrated to remove most of the DMF. This residue was dissolved in EtOAc and the solution was washed with sat'd. aq. NaHCO<sub>3</sub>, H<sub>2</sub>O, and brine, and was dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was concentrated to afford 600 mg of a semisolid which was dissolved in 3 mL THF and 3 mL H<sub>2</sub>O followed by the addition of 9 mL HOAc. The clear solution was stirred overnight at RT. The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel eluting with a gradient of CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq. NH<sub>4</sub>OH (98:1.8:0.2 to 92:7.2:0.8) to afford the semi-pure diastereomers (at \*) Compounds 312d and 313. The faster moving diastereomer was repurified by preparative TLC on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq. NH<sub>4</sub>OH (90:9:1) to afford 57 mg (14% yield) of the title Compound 312d (white solid).

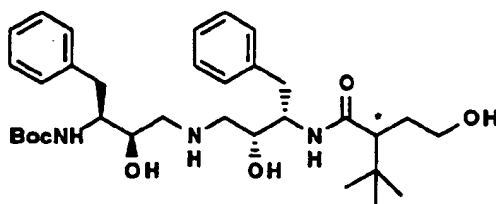
TLC R<sub>f</sub> (SiO<sub>2</sub>) = 0.19 (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq. NH<sub>4</sub>OH 90:9:1); m.p. 158-162°C ("softening" at 150-157°C); [α]<sub>D</sub> = 0.57°; (c=1.23, CH<sub>3</sub>OH)

Mass Spec. (FAB), 586 (M+H<sup>+</sup>)

Analysis calc. for C <sub>33</sub> H <sub>51</sub> N <sub>3</sub> O <sub>8</sub> ·0.05H <sub>2</sub> O:			
	C, 67.56;	H, 8.78;	N, 7.16;
Found:	C, 67.45;	H, 8.69;	N, 7.27.

Example 313

Preparation of [1S-[1R\*, 2S\* (2S\*, 3R\*)]]-[3-[[3-[[2-(1,1-Dimethylethyl)-4-hydroxy-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 313)



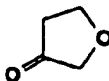
Compound 313 (white solid) was prepared as the slower moving isomer as described in Example 312. TLC R<sub>f</sub> (SiO<sub>2</sub>) = 0.13 (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq. NH<sub>4</sub>OH 90:9:1); mp 140-143°C; [α]<sub>D</sub> = -5.62°; (c=1.30, CH<sub>3</sub>OH)

Mass Spec. (FAB), 586 (M+H<sup>+</sup>)

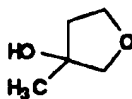
Analysis calc. for C <sub>33</sub> H <sub>51</sub> N <sub>3</sub> O <sub>8</sub> ·0.52H <sub>2</sub> O:			
	C, 66.61;	H, 8.81;	N, 7.06;
Found:	C, 66.53;	H, 8.87;	N, 7.14.

Example 314

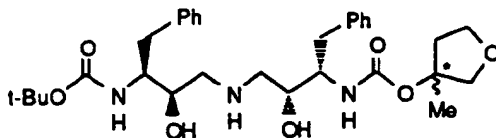
Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethyl-3-methyl-3-tetrahydrofuranylester (Compound 314c)

(a) Compound 314a

To the suspension of pyridinium chlorochromate (32 g, 0.15 mol) and activated 4Å molecular sieves (40 g, powder) in 200 ml of dry  $\text{CH}_2\text{Cl}_2$  cooled at 10°C was added a solution of 3-hydroxytetrahydrofuran (8.9 g, 0.1 mol) in 50 ml of dry  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred at RT for 2.5 h and then filtered through a short column of Florisil. The filtrate was evaporated by careful distillation of the solvent. Short-path distillation of the residue (bp: 136-137°C) afforded 4.9 g (56%) of Compound 314a as a colorless liquid.

(b) Compound 314b

Compound 314a was converted to Compound 314b by a procedure analogous to that of Example 258a.

(c) Compound 314c

(1:1 mixture of diastereomers at \*)

Compounds 314b and 48 were converted to the title Compound 314c (white solid) by a three-step procedure analogous to that used for the conversion of Compound 149c to Compound 150 (DMF was used in the coupling of the p-nitrophenyl carbonate of Compound 314b with Compound 48).

m.p.: 166-167°C.

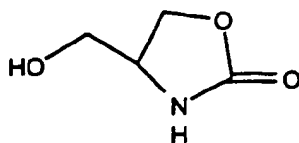
Mass Spec. (FAB): 572<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for  $\text{C}_{31}\text{H}_{45}\text{N}_3\text{O}_7 \cdot 0.18\text{H}_2\text{O}$ :

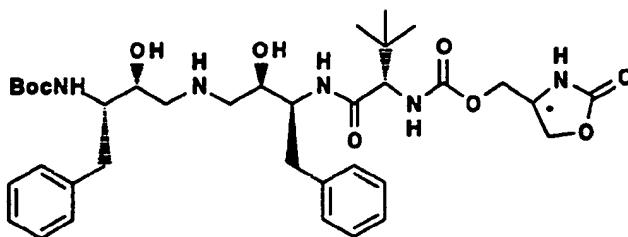
	C, 64.75;	H, 7.95;	N, 7.31.
Found:	C, 64.77;	H, 8.00;	N, 7.29.

Example 315

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]aminocarbonyl]propyl]carbamic acid, (2-oxo-4-oxazolidinyl)methyl ester (Compound 315b)

(a) Compound 315a

To a stirring solution of 2-amino-1,3-propanediol (1.58 g, 0.017 mol) in aqueous 1.73 M KOH at 0°C (20 mL) was added a toluene solution of phosgene (11 mL, 0.021 mol). After warming to RT slowly overnight, the reaction mixture was extracted with hexanes and the aqueous layer evaporated at ~30°C to give an oily solid residue. The residue was repeatedly washed with hot EtOAc and the combined washes were evaporated *in vacuo*. The resulting solid residue was co-evaporated with heptane to afford Compound 315a as a colorless solid (1.28 g, 63%).

(b) Compound 315b

(1:1 mixture of isomers at •)

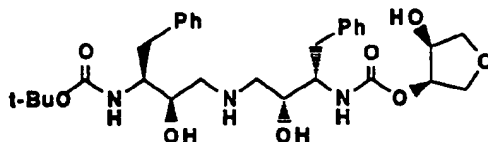
tert-Leucine and Compounds 315a and 54 were reacted by a three-step procedure analogous to that used for Example 257a through 257c to give the title Compound 315b (colorless solid).  
m.p. 104-114°C;  $[\alpha]_D = 16.6^\circ$  (c 0.22, MeOH).

Mass Spec.: (FAB): 700 (M+H).

Analysis Calc. for $C_{38}H_{53}N_5O_9$ :			
	C, 61.78;	H, 7.63;	N, 10.01
Found:	C, 61.62;	H, 7.91;	N, 9.65.

Example 316

Preparation of [1S-(1R\*,2S\*), (3S-trans)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbam-ic acid], 4-hydroxy-3-tetrahydrofuranyl 1,1-dimethylethyl ester (Compound 316)



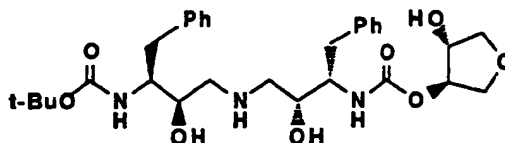
1,4-Anhydro-L-thr itol was converted to its mono-p-nitrophenyl carbonate which was reacted with Compound 48 by a procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48) to give the title Compound 316 (white solid).  
m.p.: 183-184°C;  $[\alpha]_{365} = -27.2^\circ$  (c 0.2, MeOH)

Mass Spec. (FAB): 574<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for C <sub>30</sub> H <sub>43</sub> N <sub>3</sub> O <sub>8</sub> :			
	C, 62.81;	H, 7.55;	N, 7.32.
Found:	C, 62.77;	H, 7.72;	N, 7.25.

#### Example 317

Preparation of [1S-(1R\*,2S\*), (3R-trans)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 4-hydroxy-3-tetrahydrofuranyl 1,1-dimethylethyl ester (Compound 317)



1,4-Anhydro-D-threitol (prepared from D-threitol [Terfort, *Synthesis*, 951 (1992)] according to Otey et al., *J. Org. Chem.*, 26, 1673 (1961)) was converted to its mono-p-nitrophenyl carbonate which was reacted with Compound 48 by a procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48) to give the title Compound 317 (white solid).

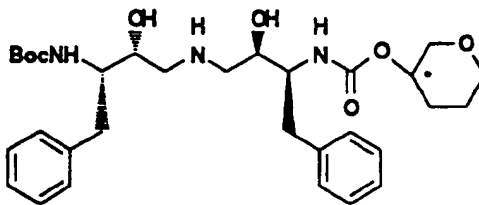
m.p.: 181-182°C; [α]<sub>D</sub> = -31.3° (c 0.63, MeOH).

Mass Spec. (FAB): 574<sup>+</sup> (M+H)<sup>+</sup>.

Analysis Calc. for C <sub>30</sub> H <sub>43</sub> N <sub>3</sub> O <sub>8</sub> ·0.45H <sub>2</sub> O:			
	C, 61.93;	H, 7.61;	N, 7.22.
Found:	C, 62.01;	H, 7.55;	N, 7.14.

#### Example 318

Preparation of [1S-(1R\*,2S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl-3-tetrahydropyranyl ester (Compound 318)



(1:1 mixture of isomers at •)

3-Hydroxytetrahydropyran (Zweifel et al., *J. Org. Chem.*, 35, 898-902 (1970)) and Compound 48 were reacted by a procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48) to give the title Compound 318 (colorless solid).

m.p. 185-187°C; [α]<sub>D</sub> = -1.80° (c 0.36, CHCl<sub>3</sub>).

MS: (FAB): 572 (M+H).

Anal. Calc. for  $C_{31}H_{45}N_3O_7 \cdot 0.09 H_2O$

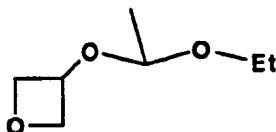
C, 64.95; H, 7.94; N, 7.35

Found: C, 64.68; H, 8.00; N, 7.33.

# Example 319

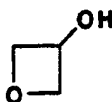
Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl 4-oxetanyl ester (Compound 319c)

## (a) Compound 319a



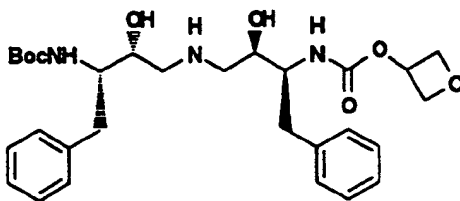
Compound 319a was prepared as described in Baum et al., *J. Org. Chem.*, 48, 2953-2956 (1983).

## (b) Compound 319b



To a solution of Compound 319a (670 mg, 4.58 mmol) in MeOH (7 mL) was added pyridinium p-tosylate (277 mg, 5 mmol). After 4 h  $NaHCO_3$  (150 mg) was added and the volatiles were evaporated *in vacuo* to give an oily solid residue which was purified by flash chromatography (silica gel, 3 by 15 cm), eluting with MeOH:CH<sub>2</sub>Cl<sub>2</sub> (3 and then 3.5% MeOH) to give Compound 319b (148 mg, 44%) as an oil.

## (c) Compound 319c



Compounds 319b and 48 were reacted by a procedure analogous to that used for the conversion of Compound 149c to 150 (DMF was used in the coupling of the p-nitrophenyl carbonate with Compound 48) to give the title Compound 319c (colorless solid).

m.p. 196-199°C;  $[\alpha]_D = -9.06^\circ$  (c 0.23, MeOH).

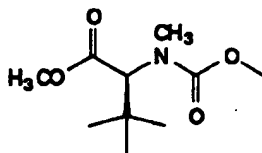
Mass Spec.: (FAB): 544 (M+H).

Analysis Calc. for  $C_{28}H_{41}N_3O_7$ :

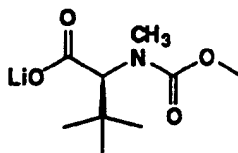
	C, 64.07;	H, 7.60;	N, 7.73
Found:	C, 63.99;	H, 7.74;	N, 7.63.

**Example 320**

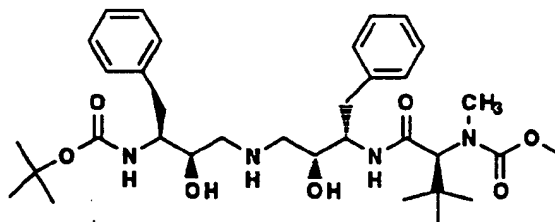
Preparation of [S-[1R\*,2S\*,(2S\*,3R\*)]-[2,2-Dimethyl-1-[[[3-[[3-(1,1-dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-carbonyl]propyl]methylcarbamic acid, methyl ester (Compound 320c)

**(a) Compound 320a**

Compound 246a was converted to Compound 320a by a procedure analogous to that of Example 66a.

**(b) Compound 320b**

Compound 320a was converted to Compound 320b by a procedure analogous to that of Example 70c (no acid work-up).

**(c) Compound 320c**

Compounds 320b and 54 were reacted by a procedure analogous to that of Example 93f to give the title Compound 320c (white solid).

m.p. = 78-81°C

Mass Spec. (CI): (M+H) = 629

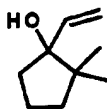
Analysis Calc. for C <sub>34</sub> H <sub>52</sub> N <sub>4</sub> O <sub>7</sub> · 1.35 H <sub>2</sub> O:			
	C,62.52;	H,8.44;	N,8.58
Found:	C,62.74;	H,8.27;	N,8.36.

**Example 321**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]-[3-[[[2,2-Dimethyl-1-hydroxycyclopentyl]-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 321d)

(a) Compound 321a

5

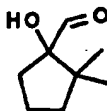


10 A suspension of anhydrous cerium (III) chloride (4.25 g; 17 mmol) in freshly distilled THF was stirred at RT for 2 h. After cooling this suspension to  $-78^{\circ}\text{C}$ , vinylmagnesium bromide (17 ml 1.0M in THF; 17 mmol) was added dropwise over  $\sim 15$  min. The resulting light orange suspension was stirred at  $-78^{\circ}\text{C}$  for 1.5 h. After this time 2,2-dimethylcyclopentanone (1.27 g; 11 mmol) was added and the reaction mixture was stirred for 1.5 h at  $-78^{\circ}\text{C}$ . Saturated  $\text{NH}_4\text{Cl}$  solution (50 ml) was added and the mixture was allowed to warm to RT with stirring.

15 The mixture was partitioned between  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$ . The organic layer was washed with  $\text{H}_2\text{O}$  and brine, dried ( $\text{MgSO}_4$ ), and most of the solvent removed *in vacuo* to afford 3.38 g of a light yellow liquid. This liquid was  $\sim 50\%$  by wt. a solution of Compound 321a in THF and was used in the subsequent step without further purification.

20 (b) Compound 321b

25

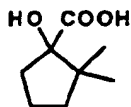


Ozone/oxygen was bubbled through a solution of Compound 321a (1.6 g; 50% by wt. in THF; 5.6 mmol) and  $\text{NaHCO}_3$  (42 mg) in 50 ml of MeOH at  $-78^{\circ}\text{C}$  for  $\sim 10$  min. After purging the solution for 15 min,  $\text{Me}_2\text{S}$  (4.5 ml) was added. After warming to RT, the mixture was stirred for 1 h and the volatiles removed *in vacuo*. The residue was partitioned between  $\text{Et}_2\text{O}$  and  $\text{H}_2\text{O}$  and the organic layer washed with brine and dried ( $\text{MgSO}_4$ ). Concentration afforded 760 mg (96%) of Compound 321b as a colorless liquid.

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35 (c) Compound 321c

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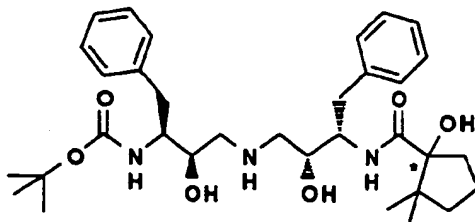
Sodium chlorite (746 mg; 6.6 mmol; 80% pure) was added to a rapidly stirring mixture of Compound 321b (720 mg; 5.06 mmol) and sulfamic acid (641 mg; 6.6 mmol) in 5 ml of  $\text{H}_2\text{O}$  and 5 ml of THF at  $0^{\circ}\text{C}$ . After stirring at  $0^{\circ}\text{C}$ . for 30 min, 0.5 ml of  $\text{Me}_2\text{S}$  was added followed by 20 ml of 1N NaOH. This mixture was extracted with  $\text{Et}_2\text{O}$  and the aqueous layer acidified to pH  $\sim 1.5$  with saturated  $\text{KHSO}_4$ , saturated with NaCl, and extracted with  $\text{EtOAc}$ . The combined organic extracts were washed with brine and dried ( $\text{MgSO}_4$ ). Concentration afforded a solid which was recrystallized from hexane to afford 456 mg (57%) of Compound 321c as a colorless solid.

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50 (b) Compound 321d

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BOP-reagent (265 mg; 0.60 mmol) was added in a portion to a solution of Compound 321c (90 mg; 0.569 mmol), Compound 54 (252 mg; 0.569) and N-methylmorpholine (66  $\mu$ l; 0.60 mol) at 0°C. in 1 ml of DMF. The reaction mixture was allowed to warm to RT and stir 16 h. After diluting with EtOAc, the organic phase was washed with H<sub>2</sub>O, saturated aq. NaHCO<sub>3</sub> and brine. After drying (MgSO<sub>4</sub>), the solvent was removed in *vacuo*. The residue was chromatographed on a 5 x 12 cm silica gel column eluting with 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> followed by a gradient of 3-7% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.3-0.7% NH<sub>4</sub>OH in 0.5% and 0.05% increments respectively. The slower moving isomer (at \*) was rechromatographed on a 2.5 x 15 cm silica gel column with elution as above followed by trituration with Et<sub>2</sub>O which afforded 23 mg (7%) of Compound 321d as a white solid.

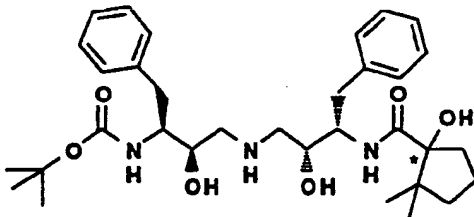
$R_f$  = 0.25, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection); m.p. 108-111°C [ $\alpha$ ]<sub>D</sub> = -15.2° (c 0.25, MeOH). Mass Spec. FAB : M+H = 584.

Analysis calc. for C<sub>33</sub>H<sub>49</sub>N<sub>3</sub>O<sub>6</sub>·0.57 H<sub>2</sub>O:

	C, 66.73;	H, 8.51;	N, 7.07;
Found:	C, 66.66;	H, 8.44;	N, 7.14.

### Example 322

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[2,2-Dimethyl-1-hydroxycyclopentyl)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 322)



The faster moving isomer from Example 321d was rechromatographed on a 2.5 x 25 cm silica gel column using 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub> followed by 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub> then 2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> and finally a gradient of 3-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.3-0.5% NH<sub>4</sub>OH in 0.25% and 0.025% increments respectively. Concentration and trituration with Et<sub>2</sub>O afforded 41 mg (12%) of Compound 322 as a white solid.

$R_f$  = 0.28, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection); m.p. 185-190 °C; [ $\alpha$ ]<sub>D</sub> = +15.5° (c 0.33, MeOH). Mass Spec. FAB: M+H = 584.

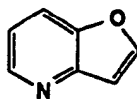
Analysis calc. for C<sub>33</sub>H<sub>49</sub>N<sub>3</sub>O<sub>6</sub>·1.17 H<sub>2</sub>O:

	C, 65.53;	H, 8.56;	N, 6.95;
Found:	C, 65.45;	H, 8.25;	N, 7.03.

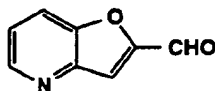
### Example 323

Preparation of (S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[3-[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-furo[3,2-b]pyridinyl)methyl ester (Compound 323f)

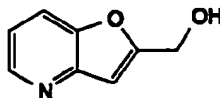


(a) Compound 323a

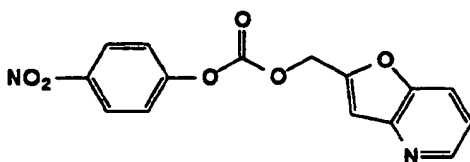
Compound 323a was prepared as described in Shiotani et al., *J. Het. Chem.*, 23, 665 (1986).

(b) Compound 323b

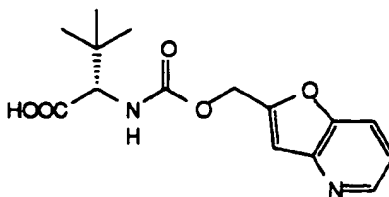
Compound 323a was converted to Compound 323b by the method described in Morita et al., *J. Heter. Chem.* 24, 373, (1987).

(c) Compound 323c

To a solution of Compound 323b (1.5 g, 10.195 mmol) in 100 mL of 3:3:4 THF-EtOH-CHCl<sub>3</sub> cooled to 0°C was added NaBH<sub>4</sub> (0.675 g, 17.841 mmol) in portions. After the addition was complete, the mixture was stirred at 0°C for 30 min, diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried (MgSO<sub>4</sub>) and concentrated. The crude residue was flash chromatographed on silica gel eluting with a stepwise gradient of 25% to 100% EtOAc-hexane to afford Compound 323c (1.42 g, 93%) as a beige solid.

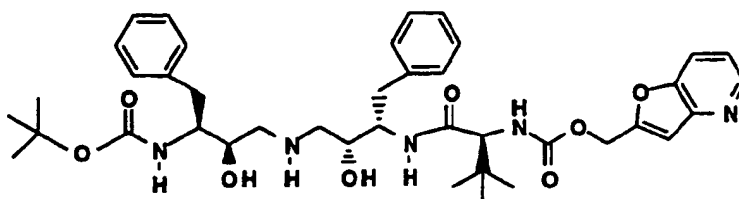
(d) Compound 323d

To a solution of Compound 323c (0.745 g, 5 mmol) in 30 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 2 mL of pyridine followed by *p*-nitrophenylchloroformate (1.008 g, 5 mmol) as a solid. The reaction mixture was stirred for 16 h at RT, diluted with EtOAc and washed with sat. NaHCO<sub>3</sub> and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to obtain Compound 323d (1.56 g, 99%; crude yield) containing traces of *p*-nitrophenylchloroformate and *p*-nitrophenol.

(e) Compound 323e

Compound 323d (0.75 g; 2.38 mmol) in 5 mL of dihexan was added to a solution of L-tert-leucine (0.314 g; 2.38 mmol) in 2.4 mL of 1N NaOH at RT followed by the addition of Et<sub>3</sub>N (365  $\mu$ L; 2.62 mmol). After 5 h at RT, the reaction mixture was diluted with 10% KHSO<sub>4</sub> and extracted with EtOAc. The organic extracts were washed with H<sub>2</sub>O and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography on silica gel of the crude residue (CH<sub>2</sub>Cl<sub>2</sub> followed by 5% then 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.5% HOAc) afforded 0.28 g (38%) of Compound 323e as a beige solid.

(f) Compound 323f



To a 0°C solution of Compound 323e (0.173 g; 0.56 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was added HOBT (0.115 g; 0.84 mmol) followed by EDCI (0.114 g; 0.59 mmol). After 30 min, Compound 54 (0.25 g; 0.56 mmol) was added followed by 0.5 mL of DMF. The reaction mixture was stirred at 0°C for 30 min and at RT for 40 h, at which time it was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub> and brine. The organic extracts were dried (MgSO<sub>4</sub>), concentrated, and the resulting residue purified by flash chromatography on silica gel, eluting with a gradient of 98.9:1:0.1 to 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, to afford 0.26 g (65%) of the title Compound 323f as a white solid.

m.p. 108-112°C. (softening at 95-105°C); [ $\alpha$ ]<sub>D</sub> = -16.5° (c = 0.2, CH<sub>3</sub>OH).

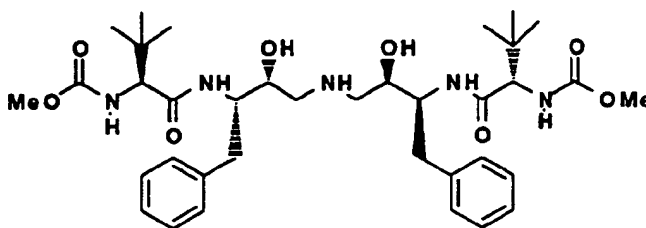
Mass Spec. (FAB) (M + H)<sup>+</sup> = 732

Analysis calc. for C<sub>40</sub>H<sub>53</sub>N<sub>5</sub>O<sub>8</sub> · 1.77H<sub>2</sub>O:

	C, 62.91;	H, 7.46;	N, 9.17;
Found:	C, 62.91;	H, 7.17;	N, 9.17.

Example 324

Preparation of 1S-(1S\*,2R\*)-N, N'-Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]bis(imino)bis[1-(1,1-dimethylethyl)-2-oxo-2,1-ethanediyl]]biscarbamic acid, dimethyl ester (Compound 324)



Compounds 74 and 246a were reacted by a procedure analogous to that of Example 75f to give the title Compound 324 (colorless solid).

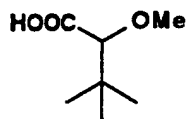
m.p. 98-102°C; [ $\alpha$ ]<sub>D</sub> = -37.7° (c 0.25, CHCl<sub>3</sub>).

Mass Spec.: (FAB): 686 (M+H).

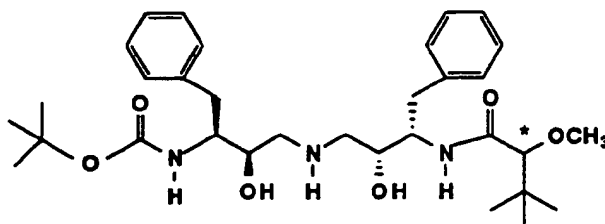
Anal. Calc. for $C_{36}H_{55}N_5O_8 \cdot 0.73 H_2O$			
	C, 61.86;	H, 8.14;	N, 10.02
Found:	C, 61.86;	H, 8.09;	N, 10.06

**Example 325**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(2-methoxy-3,3-dimethyl-1-oxobutyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 325b)

**(a) Compound 325a**

Through a solution of 4,4-dimethyl-3-methoxy-1-pentene (*J. Am. Chem. Soc.*, 109, 3353, (1987); 0.512 g, 4 mmol) in 10 mL of  $CH_2Cl_2$  cooled to  $-78^\circ C$  was bubbled  $O_3$  for a period of 2 h until a light blue color persisted. To the mixture was added  $Me_2S$  (1.468 mL, 20 mmol) and the yellow solution stirred at RT for 2 h at which point most of the solvent was distilled off. The resulting aldehyde was then converted to Compound 325a by a procedure analogous to that of Example 262e.

**(b) Compound 325b**

(1:1 mixture of isomers at \*)

Compounds 325a and 54 were reacted by a procedure analogous to that of Example 55 to give the title Compound 325b (white solid).

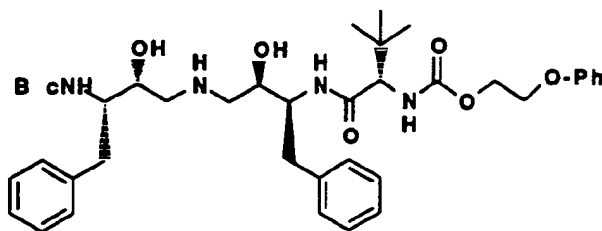
m.p.  $153-162^\circ C$ ;

Mass Spec. (FAB)  $(M + H)^+ = 572$

Analysis calc. for $C_{32}H_{49}N_3O_6 \cdot 0.58 H_2O$ :			
	C, 66.02;	H, 8.68;	N, 7.22;
Found:	C, 65.99;	H, 8.56;	N, 7.25.

**Example 326**

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-(phenyloxy)thyl) ester (Compound 326)



2-Phenoxyethanol was converted to its p-nitrophenyl carbonate which was reacted with tert-leucine and the resulting product coupled with Compound 54 by a three-step procedure analogous to that used for Example 257a through 257c to give the title Compound 326 (colorless solid).

m.p. 138-140°C (shrinks 120°C);  $[\alpha]_D = -20.4^\circ$  (c 0.3, CHCl<sub>3</sub>).

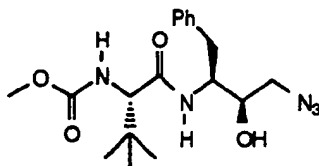
Mass Spec.: (FAB): 721 (M+H).

Anal. Calc. for C <sub>38</sub> H <sub>53</sub> N <sub>5</sub> O <sub>9</sub> · 0.31 H <sub>2</sub> O			
	C, 66.13;	H, 7.86;	N, 7.71
Found:	C, 66.09;	H, 7.85;	N, 7.75.

#### Example 327

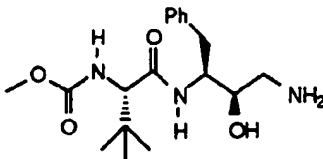
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(methoxycarbonyl)-3-methyl-L-valinamide (Compound 327c)

##### (a) Compound 327a



To an ice cooled solution, under argon, of 608 mg (2.5 mmol) of Compound 298a, 520 mg (2.75 mmol) of Compound 246a, 371 mg (2.75 mmol) of HOBT and 905  $\mu$ l of N-methylmorpholine in 12.5 ml of DMF was added 528 mg (2.75 mmol) of EDCI. Stirring was continued with cooling for 1 h, then at RT overnight. The solution was evaporated to dryness (30°C, high vacuum) and the residue taken into EtOAc and washed with brine, 1 N HCl, brine, sat. NaHCO<sub>3</sub>, and brine. After drying (MgSO<sub>4</sub>), removal of solvent afforded 1.03 g of Compound 327a as a solid white foam.

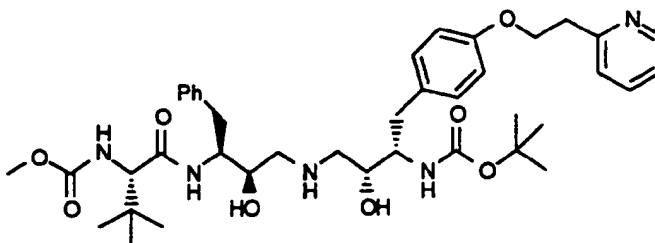
##### (b) Compound 327b



A solution of 250 mg (0.66 mmol) of Compound 327a in 8 ml of EtOH, containing 25 mg of 10% Pd on carbon catalyst, was stirred under an atmosphere of H<sub>2</sub> for 4 h. After removal of catalyst by filtration through Celite, removal of solvent gave a solid foam residue which was recrystallized from CHCl<sub>3</sub> to afford 108 mg (47% yield

ver 2 steps) of Compound 327b as a white powder.

(c) Compound 327c



A solution of 246 mg (0.70 mmol) of Compound 327b and 250 mg (0.65 mmol) of Compound 282a in 1 ml of DMF, under argon, was heated at 100°C for 5 h. The solvent was removed (30°C, high vacuum) and the residue purified by flash chromatography on a 130 cc column of silica gel. Elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (95:5:0.5) followed by recrystallization from hot EtOAc afforded 170 mg of Compound 327c as a white solid. m.p. 139–141°C; [α]<sub>D</sub> = -15.9° (c 0.92, MeOH)  
Mass Spec.: (M+H)<sup>+</sup> 736<sup>+</sup>

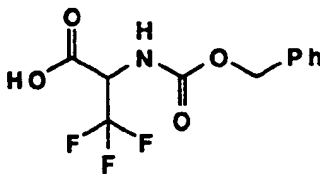
Analysis Calc. for C<sub>40</sub>H<sub>57</sub>N<sub>5</sub>O<sub>8</sub> · 0.46 H<sub>2</sub>O:

	C, 64.56;	H, 7.84;	N, 9.41.
Found:	C, 64.82;	H, 7.87;	N, 9.41.

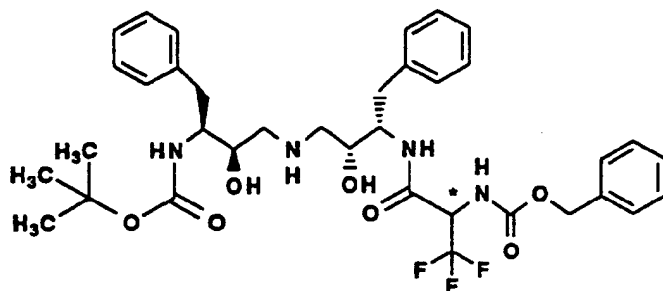
Example 328

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-[[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2-oxo-1-(trifluoromethyl)ethyl]carbamic acid, phenylmethyl ester (Compound 328b)

(a) Compound 328a



Compound 328a was prepared from D,L-trifluoromethyl alanine by a procedure analogous to that of Example 85a.

(b) Compound 328b

(1:1 mixture of isomers at \*)

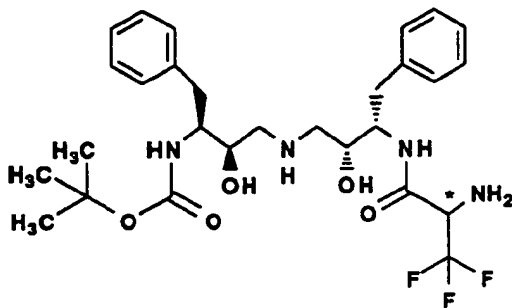
Compounds 328a and 48 were reacted by a two-step procedure analogous to that used for the conversion of Compound 48 to 52 to give the title Compound 328b (white solid).

m.p. 166-169°C;  $[\alpha]_D = -5.7^\circ$  (c = 0.21, CH<sub>3</sub>OH)

Analysis calculated for: C <sub>38</sub> H <sub>45</sub> N <sub>4</sub> O <sub>7</sub> F <sub>3</sub> · 1.21 H <sub>2</sub> O				
	C, 59.68;	H, 6.60;	N, 7.73;	F, 7.87
Found:	C, 59.74;	H, 6.47;	N, 7.67;	F, 7.81

Example 329

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1-Amino-2,2,2-trifluoroethyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 329)



(1:1 mixture of isomers at \*)

Compound 328b was converted to the title Compound 329 by a procedure analogous to that of Example 19.

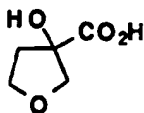
m.p. 152-155°C

Example 330

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-hydroxy-3-[[2-hydroxy-3-[(tetrahydro-3-hydroxy-3-furanyl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 330b)

(a) Compound 330a

5

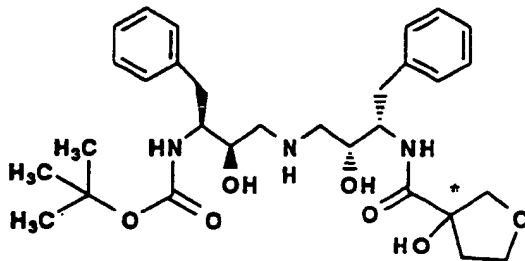


10 To a solution of Compound 314a (2.02 g, 23.46 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.5 mL) was added trimethylsilyl cyanide (4.06 mL, 30.50 mmol),  $\text{ZnI}_2$  (0.22 g, 0.70 mmol) and the solution stirred at RT for 18 h. The reaction mixture was purged with a stream of nitrogen, concentrated *in vacuo* and taken in concentrated HCl (6 mL) and heated at reflux for 2 h. After cooling to RT, the mixture was saturated with  $\text{Na}_2\text{SO}_4$  and extracted with EtOAc, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to yield a brown gummy oil. The crude product was combined with another batch (1.06 g, 12.3 mmol) of similar crude material and partially purified by silica gel chromatography, eluting with  $\text{CH}_3\text{OH}$  (5% to 60%)- $\text{CH}_2\text{Cl}_2$  (With 1 to 2% HOAc). The product was taken in 3N NaOH and washed with  $\text{Et}_2\text{O}$ . The aqueous layer was acidified to pH ca. 2 by addition of 6N HCl, saturated with  $\text{Na}_2\text{SO}_4$ , and extracted repeatedly with EtOAc. The combined organic layer was dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to afford Compound 330a (2.5 g, 52% overall yield) as a brown oil.

20

(b) Compound 330b

25



30

(1:1 mixture of diastereomers at \*)

35 Compounds 330a and 54 were reacted by a procedure analogous to that of Example 262f to give the title Compound 330b.

m.p. 119-122°C;  $[\alpha]_D = -3.5^\circ$  (c = 0.2,  $\text{CH}_3\text{OH}$ )

40

Analysis calculated for:  $\text{C}_{30}\text{H}_{43}\text{N}_3\text{O}_7 \cdot 0.45 \text{ H}_2\text{O}$ 

	C, 63.68;	H, 7.82;	N, 7.43
Found:	C, 63.63;	H, 7.79;	N, 7.48

45

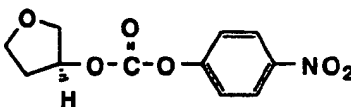
Example 331

Preparation of [1S-(1R\*,2S\*,3R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 3-tetrahydrofuranyl 1,1-dimethylethyl ester (Compound 331c)

50

(a) Compound 331a

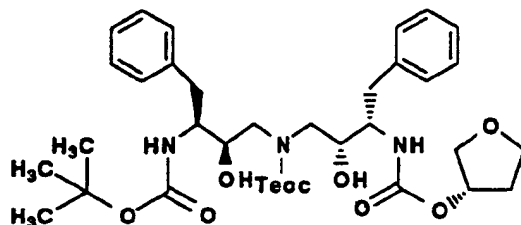
55



To a solution of (S)-(+)-3-hydroxytetrahydrofuran (441 mg, 5.0 mmol) in 15 mL of  $\text{CH}_2\text{Cl}_2$ -pyridine (5:1)

cooled at 0°C was added a solution of *para*-nitrophenylchloroformate (1.0 g, 5.0 mmol) in 12.5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred at 0°C for 1.0 h, then at RT overnight. The reaction mixture was diluted with EtOAc and the organic layer was washed with sat. aq. NaHCO<sub>3</sub> and brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Flash chromatography (hexane-EtOAc: 10:1 to 2:1) on silica gel afforded 1.25 g (99%) of Compound 331a as a colorless liquid.

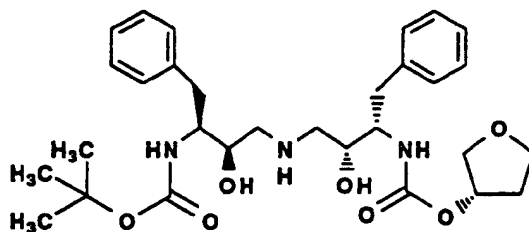
(b) Compound 331b



To a solution of Compound 48 (200 mg, 0.340 mmol) in 0.25 mL DMF was added *i*-Pr<sub>2</sub>NEt (220 mg; 1.7 mmol), followed by Compound 331a (112 mg, 0.442 mmol) in DMF (0.3 mL). After stirring overnight at RT, the reaction was concentrated *in vacuo* and diluted with EtOAc. After washing with aq. 1N NaOH, sat. aq. NaHCO<sub>3</sub> and brine, the organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel, eluting with a gradient from 0.5-5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to afford 0.2 g (83%) of a yellow foam.

Mass Spec. (Fab): (M + H)<sup>+</sup> 702<sup>+</sup>.

(c) Compound 331c



To Compound 331b (200 mg, 0.284 mmol) in THF (2 mL) was added solid *n*-Bu<sub>4</sub>NF·nH<sub>2</sub>O (223 mg, 0.854 mmol) and the mixture stirred at 50°C for 5h. The reaction was concentrated *in vacuo*, the residue dissolved in EtOAc, and washed with sat. aq. NaHCO<sub>3</sub> and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a solid which was purified by flash chromatography on silica gel, eluting with a gradient from 98.5:1.5:0.15 to 92.5:7.5:0.75 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, to afford the title Compound 331c (102 mg, 64%) as a white solid.

m.p. 200-202°C; [α]<sub>D</sub> = -14.5° (c = 0.2, CH<sub>3</sub>OH)

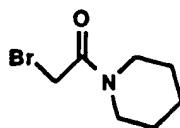
Mass Spec. (CI): (M + H)<sup>+</sup> 558.

Analysis calculated for: C <sub>30</sub> H <sub>43</sub> N <sub>3</sub> O <sub>7</sub> · 1.70 H <sub>2</sub> O			
	C, 61.08;	H, 7.96;	N, 7.12.
Found:	C, 61.10;	H, 7.45;	N, 7.10.

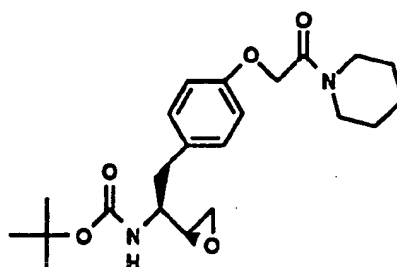
Example 332

Preparation of [1S-[1R\*,2S\* (2S\*,3R\*)]]-[3-[[[3-[[[1,1-Dimethylethoxy]carbonyl] amino]-2-hydroxy-4-[4-[2-oxo-2-(1-tetrahydropyranyl) ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl) propyl] carbamic acid, 1,1-dimethylethyl ester (Compound 332c)

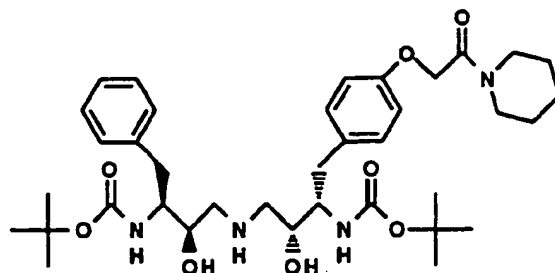


(a) Compound 332a

Bromoacetyl bromide (0.87g, 10 mmol) was added dropwise to a stirring solution of piperidine (2.03 ml, 20.60 mmol) in anhydrous Et<sub>2</sub>O (21 ml) at 0°C. After 20 min, the reaction was filtered, and the solid washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* and the crude material chromatographed on a CC<sub>7</sub> column, eluting with EtOAc, to afford 1.27g (62%) of Compound 332a as a yellow oil.

(b) Compound 332b

Compounds 175c and 332a were reacted by a procedure analogous to that of Example 226a to give Compound 332b.

(c) Compound 332c

Compounds 16b and 332b were reacted by a procedure analogous to that of Example 226b to give the title Compound 332c (colorless solid).

m.p. 116-118°C;  $[\alpha]_D = -6.0^\circ$  (c, 0.10 MeOH).

Mass spec.: (M + H) 685.

Analysis calc. for C<sub>37</sub>H<sub>56</sub>N<sub>4</sub>O<sub>8</sub> · 0.53H<sub>2</sub>O.

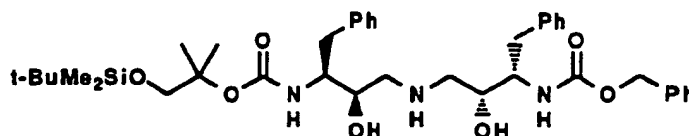
	C, 64.00;	H, 8.28;	N, 8.07;
Found:	C, 64.05;	H, 8.43;	N, 8.02.

Exempl 333

Preparation of [1S-[1R\*,2S\*,3R\*(S\*)]]-[3-[[[3-[(2-Hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ster

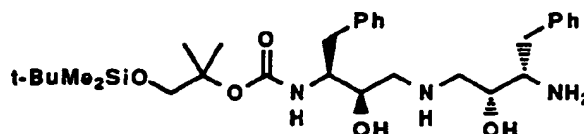
## (Compound 333d)

## (a) Compound 333a



To a solution of Compound 298c (380 mg, 0.93 mmol) in DMF (0.5 mL) was added Compound 44a (276 mg, 0.93 mmol) and the solution heated at 100°C for 4 h. The reaction mixture was cooled to RT and DMF removed *in vacuo*. Purification by silica gel chromatography, eluting with a stepwise gradient from 99.5:0.5:0.05 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq.NH<sub>4</sub>OH afforded Compound 333a (367 mg, 55% yield) as a white residue. Mass Spec: (M+H)<sup>+</sup> = 708.

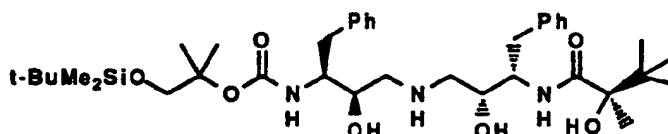
## (b) Compound 333b



To a solution of Compound 333a (365 mg, 0.52 mmol) in EtOH (14 mL) and EtOAc (3.5 mL) was added 20% Pd(OH)<sub>2</sub>/C (110 mg total added in three portions over the reaction) and the slurry stirred under a H<sub>2</sub> atmosphere overnight. Filtration, evaporation, and trituration of the resulting solid gave Compound 333b (230 mg, 77% yield) as a white solid.

Mass Spec: (M+H)<sup>+</sup> = 574

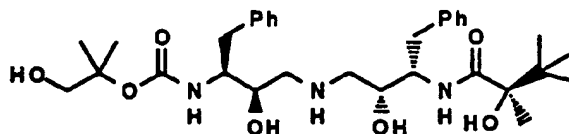
## (c) Compound 333c



To a solution of Compound 333b (127 mg, 0.22 mmol) in DMF (0.25 mL) was added a solution of Compound 262e (35.6 mg, 0.243 mmol) in 0.25 mL DMF, followed by BOP reagent (107.5 mg, 0.243 mmol) and N-methylmorpholine (53.45 μL) and the reaction stirred for 36 h. The DMF was evaporated *in vacuo* and the residue dissolved in EtOAc which was washed with satd. NaHCO<sub>3</sub> and brine and dried (MgSO<sub>4</sub>). Silica gel chromatography eluting with a stepwise gradient from 98:2:0.2 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq.NH<sub>4</sub>OH afforded Compound 333c (105 mg, 67% yield) as a solid.

Mass Spec: (M+H)<sup>+</sup> = 702

## (d) Compound 333d



To a solution of Compound 333c (103 mg, 0.146 mmol) in THF (1.5 mL) was added H<sub>2</sub>O (0.5 mL) and HOAc (0.5 mL) and the reaction mixture stirred at RT for 2 d. Evaporation to dryness, azeotropic with H<sub>2</sub>O and purification by silica gel chromatography eluting with a stepwise gradient from 98:2:0.2 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq.NH<sub>4</sub>OH afforded the title Compound 333d (74 mg, 86% yield) as a white solid.

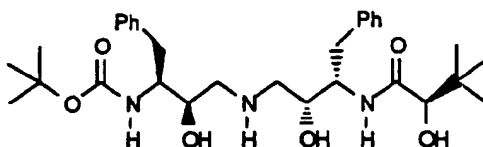
m.p. 185-188°C;  $[\alpha]_D = +19.5^\circ$  (c = 0.2, CH<sub>3</sub>OH)  
 Mass sp c. (Cl): (M + H)<sup>+</sup> 588<sup>+</sup>.

Analysis calc. for: C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>7</sub> · 0.75 H<sub>2</sub>O

	C, 63.93;	H, 8.47;	N, 6.99
Found:	C, 63.93;	H, 8.32;	N, 7.11

#### Example 334

Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(S\*)]]]-[3-[[3-[(2-Hydroxy-3,3-dimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 334)



To an ice cooled solution of 73 mg (0.55 mmol) of (R)-3,3-dimethyl-2-hydroxybutanoic acid (Ito et al., *Synthesis*, 137 (1993)), 244 mg (0.55 mmol) of Compound 54, 111 mg (0.83 mmol) of HOBT and 121  $\mu$ l (1.1 mmol) of N-methylmorpholine was added 105 mg (0.55 mmol) of EDCI as a solid. Stirring was continued with cooling for 1 h, then at RT overnight. The resulting solution was then added with stirring to an ice-sat. NaHCO<sub>3</sub> mixture. The resulting precipitate was filtered and washed with H<sub>2</sub>O. The crude product was taken into CH<sub>2</sub>Cl<sub>2</sub>, dried (MgSO<sub>4</sub>), and the solution placed on a 50 cc column of silica gel. Elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (95:5:0.5) afforded impure product. This material was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> and then rechromatographed on a 100 cc column of silica gel. A gradient elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (95:5:0.1 to 0.5) afforded 20 mg of Compound 334 as a white powder.

m.p. 175-176°C;  $[\alpha]_D = +1.1^\circ$  (c 0.08, MeOH).

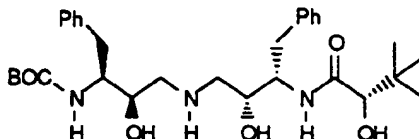
Mass Spec.: (M+H)<sup>+</sup> 558<sup>+</sup>

Analysis Calc. for C<sub>31</sub>H<sub>47</sub>N<sub>3</sub>O<sub>6</sub> · 0.25 H<sub>2</sub>O:

	C, 66.23;	N, 8.52;	N, 7.47.
Found:	C, 66.23,	H, 8.46;	N, 7.39.

#### Example 335

Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(R\*)]]]-[3-[[3-[(2-Hydroxy-3,3-dimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 335)



Compound 335 (white solid) was prepared from (S)-3,3-dimethyl-2-hydroxybutanoic acid and Compound 54 by a procedure analogous to that of Example 334.

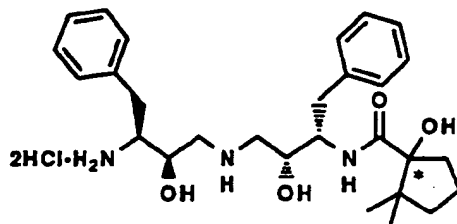
m.p.: 92-96°C;  $[\alpha]_D = -2.7^\circ$  (c 0.81, MeOH).

Mass Sp c.: (M+H)<sup>+</sup> 558<sup>+</sup>

Analysis Calc. for $C_{31}H_{47}N_3O_6 \cdot 1.0 H_2O$ :			
	C, 64.60;	N, 8.58;	N, 7.29.
Found:	C, 64.60,	H, 8.57;	N, 7.02.

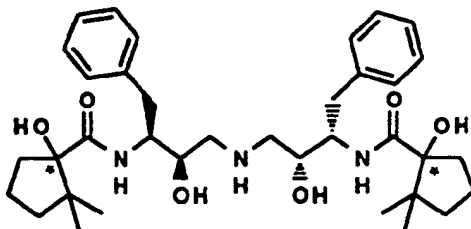
**Example 336**

**Preparation of N, N'-[Iminobis[(1S,2R)-2-Hydroxy-1-(Phenylmethyl)-3,1-propanediyl]]bis-[1-hydroxy-2,2-dimethylcyclopentanecarboxamide], isomer A (Compound 336b)**

**(a) Compound 336a**

A solution of Compound 321d (115 mg; 0.197 mmol) in 3 ml of HCl saturated EtOAc was stirred 1 h at 0°C. The volatiles were removed *in vacuo* to afford 109 mg (99%) of Compound 336a as an off-white solid.

$^1H$  NMR ( $CD_3OD$ ):  $\delta$  0.82 (s, 3H), 0.94 (s, 3H), 1.65 (m, 5H), 2.05 (m, 1H), 2.80 (dd,  $J = 10.5, 13.5$  Hz, 1H), 2.91 (dd,  $J = 8.5, 14.5$  Hz, 1H), 3.04 (m, 3H), 3.22 (m, 3H), 3.70 (m, 1H), 3.90 (m, 1H), 4.03 (m, 1H), 4.25 (m, 1H), 7.33 (m, 10H).

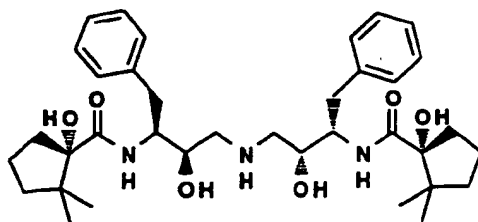
**(b) Compound 336b**

BOP-reagent (89 mg; 0.200 mmol) was added in one portion to a solution of Compound 336a (105 mg; 0.189 mmol), Compound 321c (30 mg; 0.190) and N-methylmorpholine (65 ml; 0.580 mol) at 0°C in 0.5 ml of DMF. The reaction mixture was allowed to warm to RT and stir 18 h. After diluting with EtOAc, the organic phase was washed with  $H_2O$ , saturated  $NaHCO_3$  solution and brine. After drying ( $Na_2SO_4$ ), the solvent was removed *in vacuo*. The residue was preabsorbed on celite and chromatographed on a 2.5 x 15 cm silica gel column eluting with  $CH_2Cl_2$ ; 1% MeOH/ $CH_2Cl_2$ ; 2% MeOH/ $CH_2Cl_2$ ; 2.5% MeOH/ $CH_2Cl_2$ ; then 3-5% MeOH/ $CH_2Cl_2$  + 0.3-0.5%  $NH_4OH$  in 0.25% and 0.025% increments respectively to afford 14.4 mg (12%) of Compound 336b (white solid) as a single symmetrical isomer of undetermined absolute configuration.

m.p. 135-145°C;  $R_f = 0.25$ ,  $CH_2Cl_2$ :MeOH: $NH_4OH$ , 90:9:1 (UV and PMA detection);  $[\alpha]_D^{25} = +28.2^\circ$  (c 0.38, MeOH). Mass Spec.:  $M+H = 624$ .

**Example 337**

**Preparation of N, N'-[Iminobis[(1S,2R)-2-Hydroxy-1-(Phenylmethyl)-3,1-propanediyl]]bis-[1-hydroxy-2,2-dimethylcyclopentanecarboxamide], isomer B (Compound 337)**



Compound 337 was isolated as the more polar isomer from the reaction described in Example 336. Recrystallization from ether/hexane gave 18 mg (15%) of a white solid.

m.p. 109-112°C;  $R_f$  = 0.19,  $\text{CH}_2\text{Cl}_2$ :MeOH: $\text{NH}_4\text{OH}$ , 90:9:1 (UV and PMA detection);  $[\alpha]_{365} = +25.7^\circ$  (c 0.33, MeOH).

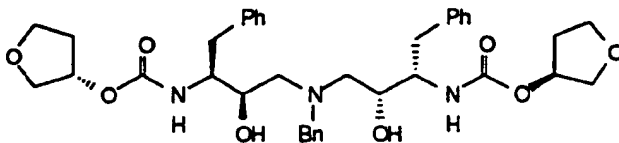
Mass Spec.:  $M+H = 624$ .

Analysis Calc. for $\text{C}_{36}\text{H}_{53}\text{N}_3\text{O}_6 \cdot 1.35 \text{ H}_2\text{O}$ :			
	C, 66.71;	N, 8.66;	N, 6.48.
Found:	C, 66.52,	H, 8.52;	N, 6.67.

#### Example 338

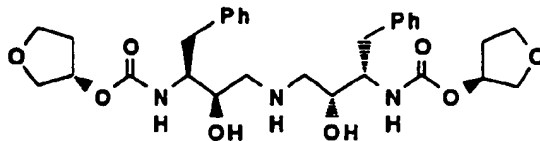
Preparation of [1S-(1R\*,2S\*), (R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], bis(3-tetrahydrofuranyl)ester (Compound 338b)

##### (a) Compound 338a



Compound 32 was reacted with 3 eq. of Compound 331a and 10 eq. of  $i\text{Pr}_2\text{NEt}$  by a procedure analogous to that of Example 149e (DMF was used in place of  $\text{CH}_3\text{CN}$ ) to give Compound 338a.

##### (b) Example 338b



Compound 338a was converted to the title Compound 338b (white solid) by a procedure analogous to that of Example 2.

m.p. 230-231°C;  $[\alpha]_D = -23.5^\circ$  (c 0.2, HOAc).

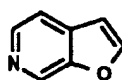
Mass Spec. (FAB): 572<sup>+</sup> ( $M+H$ )<sup>+</sup>.

Analysis Calc. for C <sub>30</sub> H <sub>41</sub> N <sub>3</sub> O <sub>8</sub> :			
	C, 63.03;	H, 7.23;	N, 7.35.
Found:	C, 63.19;	H, 7.33;	N, 7.04.

### Example 339

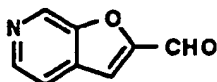
Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-furo[2,3-c]pyridinyl) methyl ester (Compound 339f)

#### (a) Compound 339a



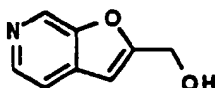
Compound 339a was prepared as described in Shiotani et al., *J. Heter. Chem.*, 19, 1207 (1982).

#### (b) Compound 339b



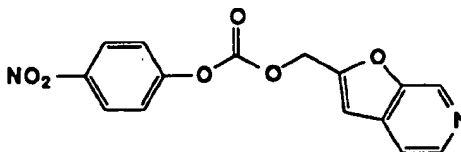
Compound 339b was prepared from Compound 339a as described in Shiotani et al., *J. Heter. Chem.*, 24, 373 (1987).

#### (c) Compound 339c



To a solution of Compound 339b (0.66 g, 4.49 mmol) in 50 mL of 3:3:4 THF-EtOH-CHCl<sub>3</sub> cooled to 0°C was added NaBH<sub>4</sub> (0.298 g, 7.86 mmol) in portions. After addition was complete, the mixture was stirred at 0°C for 30 min, diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried (MgSO<sub>4</sub>) and concentrated. The crude residue was flash chromatographed on silica gel eluting with a stepwise gradient of 25% to 100% EtOAc-hexane to afford Compound 339c (0.555 g, 83%) as a white solid.

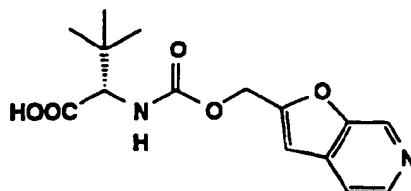
#### (d) Compound 339d



To a solution of Compound 339c (0.298 g, 2 mmol) in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> cooled to 0°C was added 1 mL of pyridine followed by *p*-nitrophenylchloroformate (0.403 g, 2 mmol) as a solid. The reaction mixture was stirred for 16 h at RT, diluted with EtOAc and washed with sat. NaHCO<sub>3</sub> and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to obtain Compound 339d (0.6 g, 95%; crude yield) containing traces of *p*-nitro-

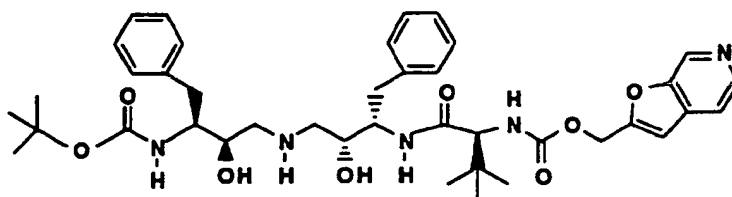
phenylchloroformate and *p*-nitrophenol.

( ) Compound 339



Compound 339d (0.6 g; 1.91 mmol) in 5 mL of dioxane was added to a solution of L-tert-leucine (0.25 g; 1.91 mmol) in 1.92 mL of 1N NaOH at RT followed by the addition of Et<sub>3</sub>N (293  $\mu$ L; 2.1 mmol). After 24 h at RT, the reaction mixture was diluted with 10% KHSO<sub>4</sub> and extracted with EtOAc. The aqueous phase was brought to pH 3.5 with 2N NaOH and extracted with EtOAc. The organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford 0.5 g (85%) of Compound 339e as an off-white solid.

(f) Compound 339f



To a 0°C solution of Compound 339e (0.173 g; 0.56 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was added HOBT (0.115 g; 0.84 mmol) followed by EDCI (0.114 g; 0.59 mmol). After 30 min, Compound 54 (0.25 g; 0.56 mmol) was added followed by 0.5 mL of DMF. The reaction mixture was stirred at 0°C for 30 min and at RT for 16 h, at which time it was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed with H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub> and brine. The organic extracts were dried (MgSO<sub>4</sub>), concentrated, and the resulting residue purified by flash chromatography on silica gel, eluting with a gradient of 96.7:3:0.3 to 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, to afford 0.135 g (33%) of the title Compound 339f as an off-white solid.

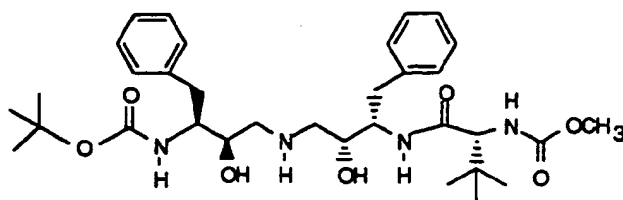
m.p. 95-105°C; [ $\alpha$ ]<sub>D</sub> = -19.4° (c = 0.2, CH<sub>3</sub>OH)

Mass Spec. (FAB) (M + H)<sup>+</sup> = 732

Analysis calc. for C <sub>40</sub> H <sub>63</sub> N <sub>5</sub> O <sub>8</sub> ·1.39H <sub>2</sub> O:			
	C, 63.42;	H, 7.43;	N, 9.25
Found:	C, 63.33;	H, 7.23;	N, 9.34.

Example 340

Preparation of [1S\*,2R\*(2R\*,3S\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)proyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-D-valinamide (Compound 340)



(D)-t-Leucine and Compound 54 were converted to the title Compound 340 by the two-step procedure described in Example 246.

m.p. 135-143°C;  $[\alpha]_D = +13.4^\circ$  (c = 0.2, CH<sub>3</sub>OH).

Mass Spec.(FAB) (M + H)<sup>+</sup> = 615

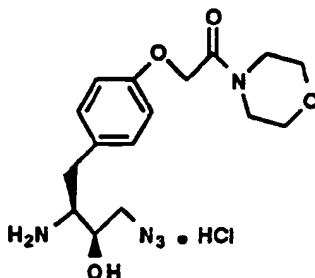
Analysis calc. for C<sub>40</sub>H<sub>63</sub>N<sub>6</sub>O<sub>8</sub>·1.39H<sub>2</sub>O:

	C, 61.95;	H, 8.31;	N, 8.76
Found:	C, 61.95;	H, 8.12;	N, 8.93.

#### Example 341

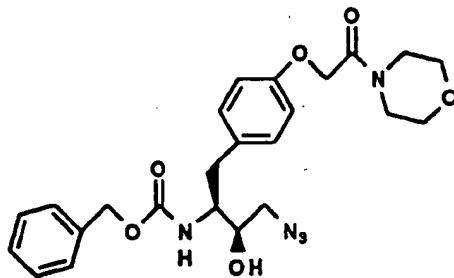
Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-[2-(4-morpholinyl)-2-oxoethoxy]phenyl]methyl]propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide (Compound 341e)

##### (a) Compound 341a



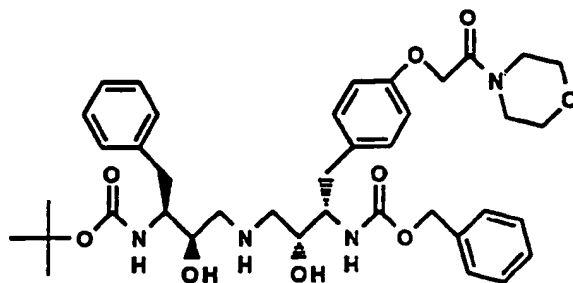
Compound 226a was converted to Compound 341a by a two-step procedure analogous to that used for the conversion of Compound 282a to Compound 282c.

##### (b) Compound 341b

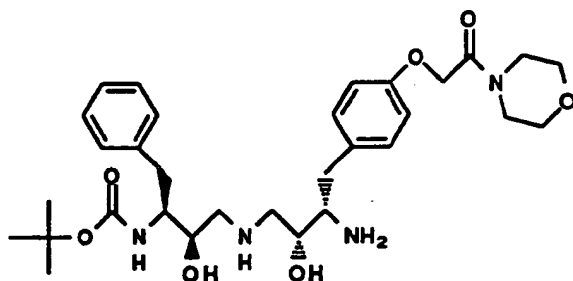


Compound 341a was converted to Compound 341b by a procedure analogous to that of Example 122 except that carbobenzyloxy chloride was used.

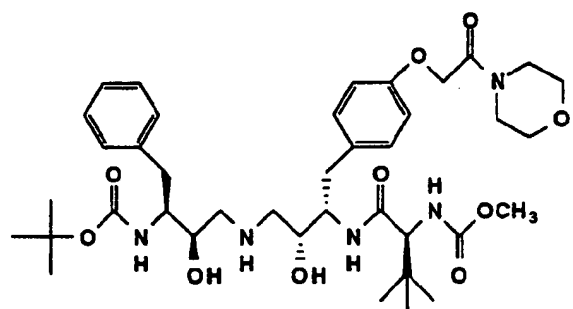


(c) Compound 341c

Compounds 341b and 1b(i) were converted to Compound 341c by a two-step procedure analogous to that used for the conversion of Compound 282d to Compound 282f.

(d) Compound 341d

Compound 341c was converted to Compound 341d by a procedure analogous to that of Example 19.

(e) Compound 341e

Compounds 341d and 246a were reacted by a procedure analogous to that of Example 246b to give the title Compound 341e (white solid).

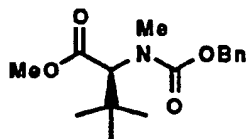
m.p. 128-130°;  $[\alpha]_D = -12^\circ$  (c=0.07, MeOH).

Mass spec.: 758<sup>+</sup> (M + H)<sup>+</sup>.

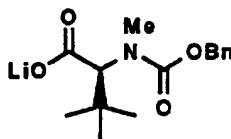
Analysis calc. for C <sub>39</sub> H <sub>69</sub> N <sub>5</sub> O <sub>10</sub> · 0.9 H <sub>2</sub> O:			
	C, 60.51;	H, 7.92;	N, 9.05;
Found:	C, 60.79;	H, 8.01;	N, 8.65.

Example 342

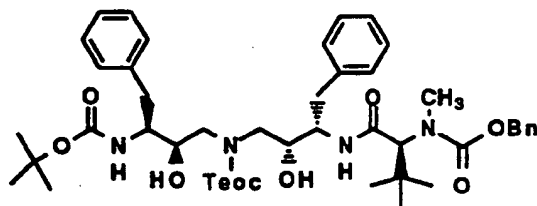
Preparation of [1R\*, 2S\* (2S\*, 3R\*)]-N-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-[(methylamino)carbonyl]-N<sup>2</sup>-3-dimethyl-L-valinamid (Compound 342f)

(a) Compound 342a

Compound 88a was converted to Compound 342a by a procedure analogous to that of Example 66a (except that DMF was used as solvent instead of THF).

(b) Compound 342b

Compound 342a was converted to Compound 342b by a procedure analogous to that of Example 70c except that the reaction was not acidified before evaporation.

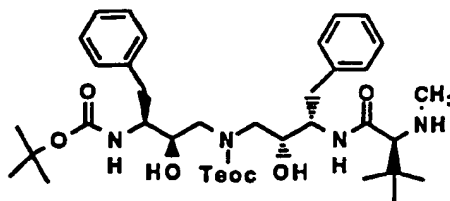
(c) Compound 342c

To a 0°C solution of Compound 48 (200 mg; 0.34 mmol) and Compound 342b (102 mg; 0.35 mmol) in anhydrous DMF (0.68 mL) were successively added BOP reagent (0.154 g; 0.350 mmol) and N-methyl morpholine (0.188 mL; 1.71 mmol). The solution was allowed to warm to RT and stirred for 36 h. Volatiles were removed *in vacuo* and the residue was partitioned between saturated aqueous NaHCO<sub>3</sub> and EtOAc. The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to give a viscous oil, which was chromatographed on silica gel using a gradient from 10% EtOAc-hexane to 50% EtOAc-hexane to furnish Compound 342c (233 mg; 81%) as a white solid.

(d) Compound 342d

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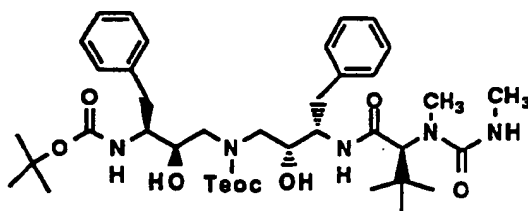
Compound 342c was converted to Compound 342d (white solid) by a procedure analogous to that of Example 19.

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(e) Compound 342e

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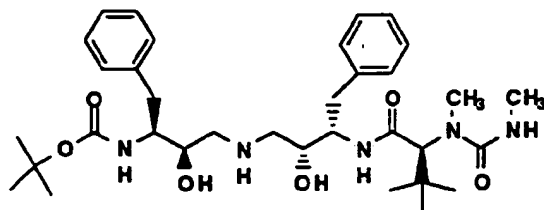
Compound 342d and methyl isocyanate were reacted by a procedure analogous to that of Example 46 to give Compound 342e (colorless oil).

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(f) Compound 342f

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Compound 342e was converted to the title Compound 342f (white solid) by a procedure analogous to that of Example 21.

m.p. 87-90°C

Mass Spec. (FAB): (M+H) = 628

45

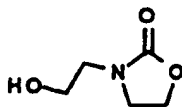
Example 343

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(2-oxo-3-oxazolidinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamic acid, 1,1-dimethylethyl ester (Compound 343c)

50

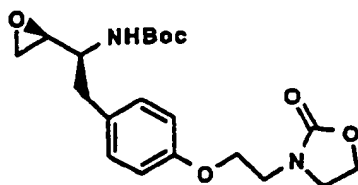
(a) Compound 343a

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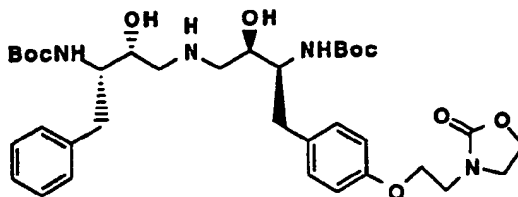
Diethanolamine was converted to Compound 343a by a procedure analogous to that of Example 315a.

(b) Compound 343b



Compounds 175c and 343a were reacted by a procedure analogous to that of Example 282a to give Compound 343b.

(c) Compound 343c



Compounds 16b and 343b were reacted by a procedure analogous to that of Example 226b (except that the reaction was run in MeOH at 60°C) to afford the title Compound 343c (colorless solid).

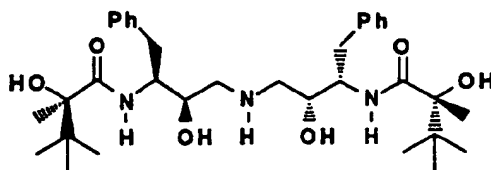
m.p. 130.5-133.5°C;  $[\alpha]_D = -3.1^\circ$  (c 0.27, MeOH).

Mass Spec.: (FAB): 673 (M+H).

Anal. Calc. for $C_{35}H_{62}N_4O_9 \cdot 0.25 H_2O$			
	C, 62.07;	H, 7.81;	N, 8.27
Found:	C, 62.04;	H, 7.84;	N, 8.29.

Example 344

Preparation of [2R-[R\*(R\*,S\*)]]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[2-hydroxy-2,3,3-trimethylbutaneamide] (Compound 344)



BOP reagent (308 mg, 0.7 mmol) was added to a stirred mixture of Compound 74 (0.15 g, 0.33 mmol), Compound 262e (0.102 g, 0.7 mmol) and N-methylmorpholine (0.254 mL, 2.32 mmol) in 0.75 mL dry DMF. The mixture was stirred at RT for 14 h, concentrated and the residue partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), concentrated, and the residue purified by flash chromatography (silica gel/CH<sub>2</sub>Cl<sub>2</sub> stepwise to 95:5:0.5 CH<sub>2</sub>Cl<sub>2</sub>-MeOH-aq NH<sub>4</sub>OH) followed by preparative HPLC (column: Polymer Labs. PLRP-S 100 A 10  $\mu$ m 25X300 mm; eluent: 1:1 A:B, eluent A = H<sub>2</sub>O-CH<sub>3</sub>CN-NH<sub>4</sub>OH 90:10:0.2, eluent B = H<sub>2</sub>O-CH<sub>3</sub>CN-NH<sub>4</sub>OH 10:90:0.2; UV 254 nm) to afford 100 mg (50%) of the title Compound 344 as a white

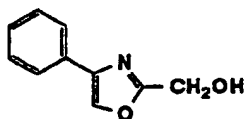
solid.

m.p. 159-160°C;  $[\alpha]_D +43.8^\circ$  (c 0.48, M OH).Mass Sp c.: 600 (M+H)<sup>+</sup>.Analysis calc. for C<sub>34</sub>H<sub>63</sub>N<sub>3</sub>O<sub>6</sub>·0.59 H<sub>2</sub>O:

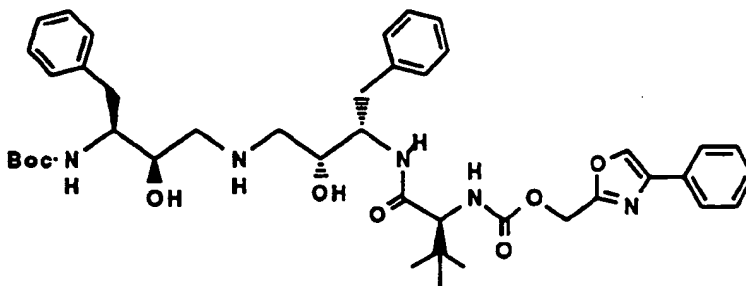
	C, 66.90;	H, 8.95;	N, 6.88.
Found:	C, 66.89;	H, 8.90;	N, 6.89.

**Example 345**

Preparation of [S-(1R\*,2S\*(2S\*,3R\*))]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (4-phenyl-2-oxazoly)methyl ester (Compound 345b)

**(a) Compound 345a**

A solution of 4-phenyloxazole (Whitney, *J. Org. Chem.*, 55, 929-935 (1990)) (2.15 g; 14.8 mmol) and 2,2,4,4-tetramethylpiperidine (250  $\mu$ l; 1.48 mmol) in 30 ml of distilled THF at -78°C was added 1.3 M *s*-BuLi in cyclohexane (13.7 ml). The mixture was stirred for 30 min at -78°C and then warmed to 0°C. Formaldehyde gas (from paraformaldehyde) was bubbled through the mixture for 5 min and it was allowed to warm to RT and stir overnight. The reaction was quenched with 1 N HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation and purification on a silica gel column eluting with EtOAc/hexane (1:3) and EtOAc/hexane (1:1) gave 1.75 g (68%) Compound 345a.

**(b) Compound 345b**

Compound 345a was converted to its *p*-nitrophenyl carbonate which was reacted with *tert*-leucine and the resulting product coupled with Compound 54 by a three-step procedure analogous to that used for Example 257a through 257c to give the title Compound 345b (colorless solid).

m.p. 178-184°C (dec.);  $[\alpha]_D = -11^\circ$  (c = 0.25, MeOH).Analysis calcd. for C<sub>42</sub>H<sub>65</sub>N<sub>5</sub>O<sub>8</sub> · 0.5 H<sub>2</sub>O:

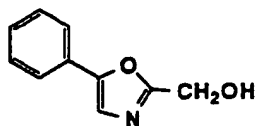
	C, 65.73;	H, 7.36;	N, 9.12
Found:	C, 65.73;	H, 7.30;	N, 9.12

Mass Spec. (FAB): (M+H)<sup>+</sup> = 758<sup>+</sup>.



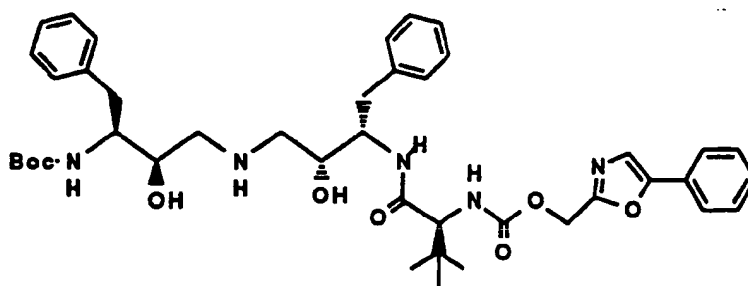
nyl-2-oxazolyl)methyl ester (Compound 347b)

(a) Compound 347a



5-Phenyloxazole-2-carboxylic acid ethyl ester (Saito, *J. Pharm. Soc. Japan*, 76, 305 (1956)) was converted to Compound 347a by a procedure analogous to that of Example 281a (except that the reaction was run at 0°C to RT).

(b) Compound 347b



Compound 347a was converted to its p-nitrophenyl carbonate which was reacted with tert-leucine and the resulting product coupled with Compound 54 by a three-step procedure analogous to that used for Example 257a through 257c to give the title Compound 347b (colorless solid).  
m.p. 168-174°C (dec.);  $[\alpha]_D = 12.5^\circ$  (c = 0.25, MeOH).  
Mass Spec. (FAB):  $(M+H)^+ = 758^+$

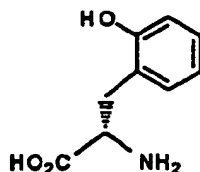
Analysis calcd. for:  $C_{42}H_{56}N_5O_8 \cdot 0.68 H_2O$ :

	C, 65.50;	H, 7.38;	N, 9.09
Found:	C, 65.46;	H, 7.29;	N, 9.13.

Example 348

Preparation of [1S-[1R\*,2S\* (2S\*,3R\*)]]-[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[2-(phenylmethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 348d)

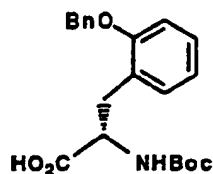
(a) Compound 348a



D,L-o-Tyrosine was resolved into the (L) enantiomer, Compound 348a, by the procedure described in *Can.*

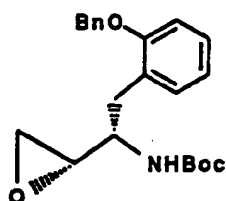
*J. Biochem.*, 49, 877 (1971).

(b) Compound 348b



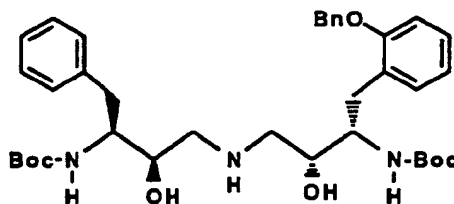
Compound 348a was converted to Compound 348b by a three-step procedure analogous to that used for the conversion of Compound 28b to Compound 28e.

(c) Compound 348c



Compound 348b was converted into Compound 348c by procedures analogous to those used for the synthesis of Compound 1b(i).

(d) Compound 348d



Compounds 348c and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 348d (colorless solid).

m.p. 146-152°C;  $[\alpha]_D = -4^\circ$  (c 0.8, HOAc)

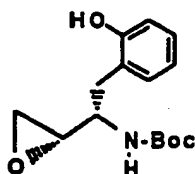
Mass Spec. (CI):  $(M+H)^+ = 650^+$

Analysis calcd. for: $C_{37}H_{51}N_3O_7 \cdot 1.5 H_2O$ :			
	C, 65.65;	H, 8.04;	N, 6.41
Found:	C, 65.49	H, 7.72;	N, 6.66.

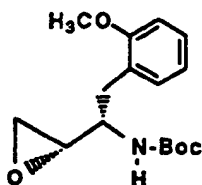
Example 349

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-1,1-Dimethylethoxy)-carbonyl]amino]-2-hydroxy-4-(2-methoxy-phenyl)butyl]-amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 349c)

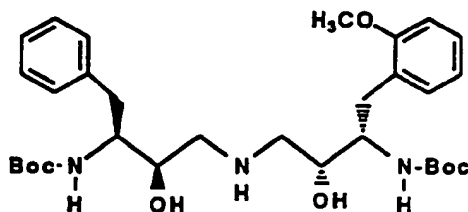


(a) Compound 349a

Compound 348c was converted to Compound 349a by a procedure analogous to that of Example 175c.

(b) Compound 349b

A solution of Compound 349a (70 mg, 0.25 mmol) in 0.5 ml of dry DMF was cooled to 0°C and 250  $\mu$ l of a 1 M solution of sodium bis(trimethylsilyl)amide in THF (46 mg, 0.25 mmol) was added. After stirring for 15 min, 10 eq. of  $\text{CH}_3\text{I}$  (0.15 ml, 2.5 mmol) was added and the resulting mixture was stirred at 0°C for 1 h and then allowed to warm to RT and stir overnight. The DMF was evaporated and the crude product purified on a 20 ml silica gel column eluting with 15% EtOAc/hexane yielding 68 mg (93%) of Compound 349b.

(c) Compound 349c

Compounds 349b and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 349c (colorless solid).

m.p. 136-140°C;  $[\alpha]_D = 3.5^\circ$  (c 0.5, HOAc)

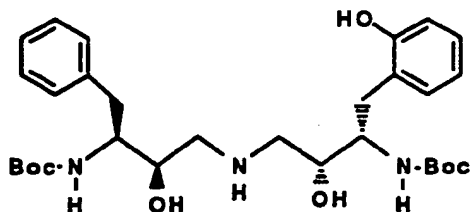
Mass Spec. (CI):  $(M+H)^+ = 574^+$

Analysis calcd. for:  $\text{C}_{31}\text{H}_{47}\text{N}_3\text{O}_7 \cdot 1.45 \text{ H}_2\text{O}$ :

	C, 62.07;	H, 8.38;	N, 7.01
Found:	C, 61.92;	H, 8.08;	N, 7.16.

Example 350

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(2-hydroxyphenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 350)



Compound 348d was converted to the title Compound 350 (colorless solid) using conditions analogous to those of Example 43.

m.p. 156-160°C;  $[\alpha]_D = -5.2^\circ$  (c 0.5, HOAc)

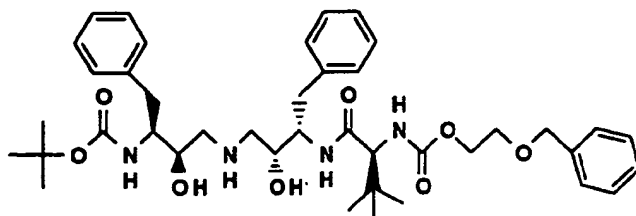
Mass Spec. (CI):  $(M+H)^+ = 560^+$

Analysis calcd. for:  $C_{30}H_{45}N_3O_7 \cdot 1.18 H_2O$ :

	C, 62.03;	H, 8.22;	N, 7.23
Found:	C, 61.95;	H, 7.79;	N, 7.31.

#### Example 351

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)-propyl]amino]carbonyl]propyl]carbamic acid, 2-(phenylmethoxy) ethyl ester (Compound 351)



2-Benzyloxyethanol was converted to its p-nitrophenyl carbonate which was reacted with tert-leucine and the resulting product coupled with Compound 54 by a three-step procedure analogous to that used for Example 257a through 257c to give the title Compound 351 (white solid).

m.p. 99-101°C;  $[\alpha]_D = -13^\circ$  (c 0.11, MeOH).

Mass spec.:  $735^+$  (M + H) $^+$ .

Analysis calc. for  $C_{41}H_{68}N_4O_8 \cdot 1.61 H_2O$ :

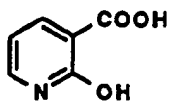
	C, 64.46;	H, 8.08;	N, 7.33;
Found:	C, 64.15;	H, 7.83;	N, 7.51.

#### Example 352

Preparation of [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)-propyl]amino]carbonyl]propyl]carbamic acid, (2-furo[2,3-b]pyridinyl)methyl ester (Compound 352h)

(a) Compound 352a

5

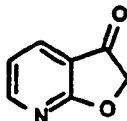


Compound 352a was prepared as described in Sliwa, *Bull Soc. Chim. Fr.* 631 (1970).

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(b) Compound 352b

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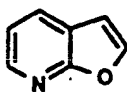


Compound 352a was converted to Compound 352b by the procedure described in Morita et al., *J. Heter. Chem.*, 23, 1465 (1986).

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(c) Compound 352c

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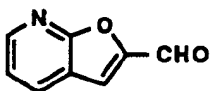


Compound 352b was converted to Compound 352c by the procedure described in Sliwa, *Bull Soc. Chim. Fr.* 646 (1970).

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(d) Compound 352d

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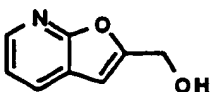


Compound 352c was converted to Compound 352d by the procedure described in Morita et al., *J. Heter. Chem.*, 23, 1465 (1986).

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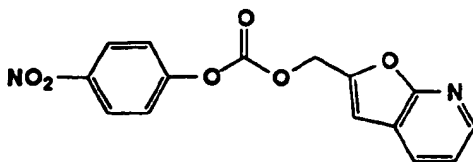
(e) Compound 352e

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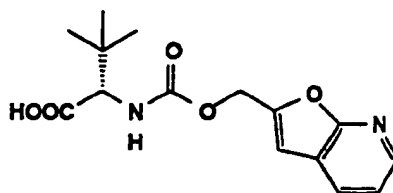


To a solution of Compound 352d (0.26 g, 1.769 mmol; ca. 75% pure) in 20 mL of 3:3:4 THF-EtOH-CHCl<sub>3</sub> cooled to 0°C was added NaBH<sub>4</sub> (0.117 g, 3.095 mmol) in portions. After addition was complete, the mixture was stirred at 0°C for 30 min, diluted with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried (MgSO<sub>4</sub>) and concentrated. The crude residue was flash chromatographed on silica gel eluting with a stepwise gradient of 25% to 100% EtOAc-hexane to afford Compound 352e (0.16 g, 80%) as a white solid.

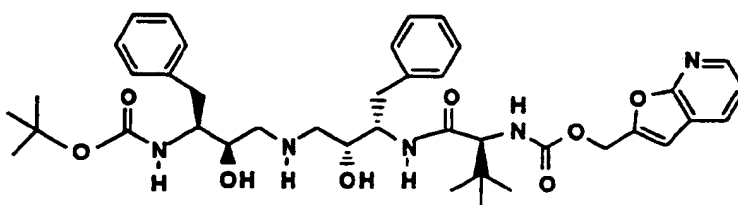
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(f) Compound 352f

To a solution of Compound 352e (0.160 g, 1.073 mmol) in 8 mL of  $\text{CH}_2\text{Cl}_2$  cooled to  $0^\circ\text{C}$  was added 0.5 mL of pyridine followed by *p*-nitrophenylchloroformate (0.216 g, 1.073 mmol) as a solid. The reaction mixture was stirred for 20 h at RT, diluted with EtOAc and washed with sat.  $\text{NaHCO}_3$  and brine. The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated to obtain Compound 352f (0.336 g, crude yield) containing traces of *p*-nitrophenylchloroformate and *p*-nitrophenol.

(g) Compound 352g

Compound 352f (0.336 g; 1.07 mmol) in 5 mL of dioxane was added to a solution of L-tert-leucine (0.154 g; 1.177 mmol) in 1.17 mL of 1N NaOH at RT followed by the addition of  $\text{Et}_3\text{N}$  (179  $\mu\text{L}$ ; 1.284 mmol). After stirring overnight at RT, the reaction mixture was diluted with 10%  $\text{KHSO}_4$  and the pH adjusted to 2.0 with 1N NaOH. The mixture was extracted with EtOAc and the combined extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography on silica gel of the crude residue ( $\text{CH}_2\text{Cl}_2$  followed by a stepwise gradient from 2% to 10%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  + 0.5% HOAc) afforded 0.23 g (ca. 80% pure) of Compound 352g.

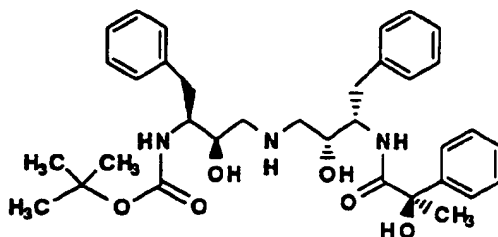
(h) Compound 352h

To a  $0^\circ\text{C}$  solution of Compound 352g (0.15 g; 0.40 mmol based on 80% pure material) in 3 mL of  $\text{CH}_2\text{Cl}_2$  was added HOBT (0.092 g; 0.676 mmol) followed by EDCI (0.091 g; 0.474 mmol). After 30 min, Compound 54 (0.20 g; 0.451 mmol) was added followed by 0.5 mL of DMF. The reaction mixture was stirred at  $0^\circ\text{C}$  for 30 min and at RT for 16 h, at which time it was diluted with EtOAc, and washed with  $\text{H}_2\text{O}$ , sat. aq.  $\text{NaHCO}_3$  and brine. The organic extracts were dried ( $\text{MgSO}_4$ ), concentrated, and the resulting residue purified by flash chromatography on silica gel, eluting with a gradient of 98.9:1:0.1 to 90.1:9:0.9  $\text{CH}_2\text{Cl}_2$ : $\text{MeOH}$ : $\text{NH}_4\text{OH}$ , to afford 0.238 g (72%) of the title Compound 352h as an off-white solid.  
m.p.  $99\text{--}106^\circ\text{C}$ ;  $[\alpha]_D^{25} = -15.2^\circ$  ( $c = 0.2$ ,  $\text{CH}_3\text{OH}$ ).  
Mass Spec. (FAB) ( $M + H$ ) $^+ = 732$

Analysis calc. for $C_{40}H_{53}N_5O_8 \cdot 1.28 H_2O$ :			
	C, 63.64;	H, 7.42;	N, 9.28
Found:	C, 63.54;	H, 7.37;	N, 9.38.

**Example 353**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[3-[(2-Hydroxy-1-oxo-2-phenylpropyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl ethyl ester (Compound 353)



To a solution of Compound 54 (100 mg, 0.225 mmol) in DMF (0.4 ml) was added a solution of (R)-2-hydroxy-2-phenylpropionic acid (41 mg, 0.247 mmol) in 0.3 ml DMF, followed by BOP reagent (109 mg, 0.247 mmol) and N-methylmorpholine (54  $\mu$ l; 0.49 mmol) to afford 55 mg (41%) the title Compound 353 using a procedure analogous to that of Example 262f.

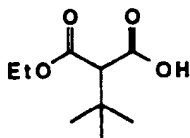
m.p. 161-163°C;  $[\alpha]_D = +2.5^\circ$  (c 0.2,  $CH_3OH$ )

Mass spectrum (Fab):  $(M + H)^+$  592 $^+$ .

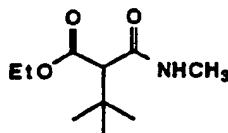
Analysis Calc. for: $C_{34}H_{46}N_3O_8 \cdot 0.51 H_2O$ :			
	C, 67.95;	H, 7.72;	N, 6.99
Found:	C, 67.92;	H, 7.48;	N, 7.02.

**Example 354**

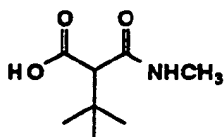
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[3,3-Dimethyl-2-[(methylamino)carbonyl]-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 354d)

**(a) Compound 354a**

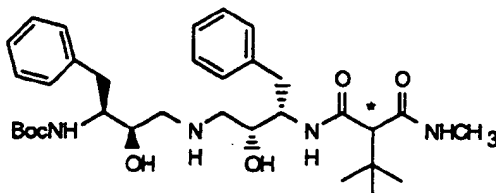
2-tert-Butyl-diethylmalonate was saponified with KOH/EtOH to afford Compound 354a as described in Bajwa et al. *J. Amer. Chem. Soc.*, 104, 6385 (1982).

(b) Compound 354b

A solution of Compound 354a (1.0 g, 5.31 mmol) in 0.775 ml (10.62 mmol) of  $\text{SOCl}_2$  was refluxed for 2 h. The excess  $\text{SOCl}_2$  was removed *in vacuo* and the residue was dissolved in 20 ml dry  $\text{Et}_2\text{O}$ . Anhydrous  $\text{CH}_3\text{NH}_2$  was bubbled into the reaction until no more precipitate formed. The precipitate was filtered off and the filtrate was concentrated to afford 865 mg (81%) of Compound 354b.

(c) Compound 354c

Compound 354c was prepared from Compound 354b by a procedure analogous to that used for the preparation of Compound 354a.

(d) Compound 354d

(1:1 mixture of isomers at \* )

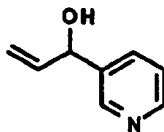
Compound 354d (white solid) was prepared as a 1:1 mixture of diastereomers from Compounds 354c and 54 by a procedure analogous to that of Example 334.  
m.p. 117-120°C ("softening" at 114-117°C)  
Mass Spec. (FAB), 599 ( $\text{M}+\text{H}^+$ )

Analysis Calc. for:  $\text{C}_{31}\text{H}_{50}\text{N}_4\text{O}_8 \cdot 0.16 \text{ H}_2\text{O}$ :

	C, 65.87;	H, 8.43;	N, 9.31
Found:	C, 65.84;	H, 8.55;	N, 9.34.

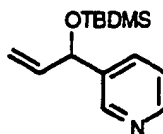
Example 355

Preparation of [1S-[1R\*,2S\* (2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-hydroxy-2-(3-pyridinyl)ethoxy]phenyl]-butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid, 1,1-dimethylethyl ester, Isomer A (Compound 355f)

(a) Compound 355a

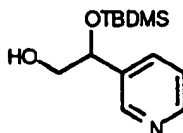
10 Pyridine 3-carboxaldehyde (4.0 g; 37.3 mmol) in THF (50 mL) was reacted with vinyl magnesium bromide (41.0 mL of a 1.0 M solution in THF; 41.0 mmol), first at 0°C then at RT for 24 h. The reaction mixture was cooled to 0°C and aqueous NH<sub>4</sub>Cl (55 mL of a 1 M solution) was slowly added, followed by EtOAc (200 mL). The resulting mixture was filtered through Celite and the aqueous layer extracted with EtOAc. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an oil, which was purified by flash chromatography (500 mL SiO<sub>2</sub>; stepwise gradient from 1:1 to 1:5 hexanes:EtOAc) to give Compound 355a (3.89 g; 77%) as a pale yellow oil.

15

(b) Compound 355b

To a 0°C solution of Compound 355a (0.40 g; 2.96 mmol) in anhydrous DMF (3.0 mL) were successively added tert-butyldimethylsilyl chloride (0.535 g; 3.55 mmol), Et<sub>3</sub>N (0.467 g; 4.62 mmol) and DMAP (0.036 g; 0.296 mmol). The mixture was allowed to warm to RT and stirred for 24 h. Volatiles were removed *in vacuo* and the residue was partitioned between aqueous NaHCO<sub>3</sub> (20 mL of a 50% saturated solution) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with H<sub>2</sub>O, dried, and concentrated *in vacuo* to give an oil. Flash chromatography (SiO<sub>2</sub>; 100 mL) using as eluent 10:1 hexane:EtOAc furnished Compound 355b (0.744; 100%) as a pale yellow oil.

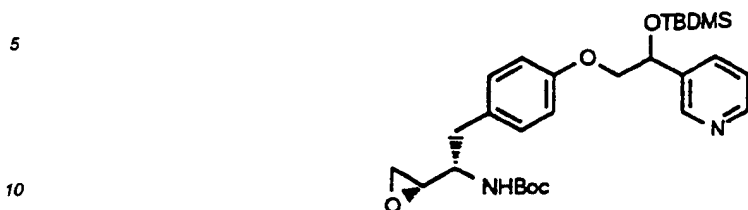
30

(c) Compound 355c

A stream of O<sub>3</sub> was bubbled into a -78°C solution of Compound 355b (0.650 g; 2.61 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) for 15 min until the solution was faintly blue. After stirring for a further 30 min at -78°C, N<sub>2</sub> was bubbled into the solution for 15 min to discharge the blue color. DIBAL-H (10.4 mL of a 1.0 M solution in hexane; 10.4 mmol) was added dropwise over 5 min, followed by 10 mL of dry hexane. The solution was stirred at -78°C for 1 h, then at -20°C for 2 h. The solution was then recooled to -78°C and MeOH (3.0 mL) was added dropwise. The solution was allowed to warm to RT and brine (5.0 mL), Et<sub>2</sub>O (100 mL) and MgSO<sub>4</sub> (15 g) were added. The mixture was stirred for 2 h, filtered, and concentrated *in vacuo* to give a yellow oil, which was flash chromatographed (SiO<sub>2</sub>; 100 mL) using a stepwise gradient from 1:1 to 1:4 hexane:EtOAc to give Compound 355c (0.234g; 35%) as a slightly yellow oil.

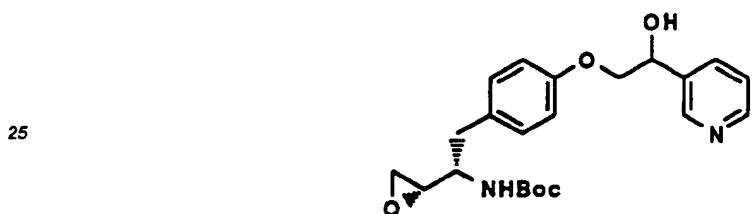
45

50

(d) Compound 355d

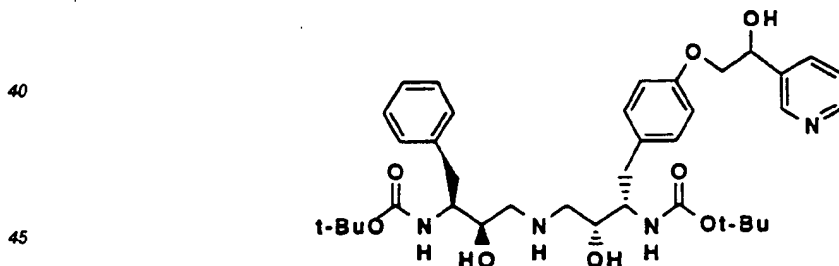
Compound 355c (0.331 g; 1.31 mmol) and Compound 175c (0.183 g; 0.655 mmol) were reacted with DEAD (0.228 g; 1.31 mmol) and  $\text{Ph}_3\text{P}$  (0.343 g; 1.31 mmol) in THF for 24 h at RT. The solution was concentrated *in vacuo* and adsorbed onto Celite. Flash chromatography (100 mL  $\text{SiO}_2$ ) using a gradient from 95:5 to 1:1 hexane:EtOAc gave Compound 355d (0.301 g; contaminated with 1,2-dicarbethoxyhydrazine; only one of two possible diastereomers was isolated) as a pale yellow viscous oil.

15

(e) Compound 355e

Compound 355d (0.301 g) was dissolved in anhydrous THF and  $n\text{-Bu}_4\text{NF}\cdot\text{H}_2\text{O}$  (0.204 g; 0.779 mmol) was added at RT. The yellow solution was stirred for 1.5 h. Volatiles were removed *in vacuo* and the residue was purified by flash chromatography ( $\text{SiO}_2$ , 100 mL) using a gradient from 1:1 to 1:10 hexane:EtOAc to give Compound 355e (0.096 g; 37% for 2 steps) as a white solid.

30

(f) Compound 355f

Compound 355e (0.030 g; 0.075 mmol) and Compound 16b (0.025 g; 0.090 mmol) were heated in MeOH (0.20 mL) at 60°C for 4 h. Volatiles were removed *in vacuo* and the residue was purified by flash chromatography on  $\text{SiO}_2$  (100 mL) using as eluent a stepwise gradient from 99:1:0.1 to 92:8:0.8  $\text{CH}_2\text{Cl}_2$ : MeOH:  $\text{NH}_4\text{OH}$  to afford a white solid (0.026 g, 52%). This material was further purified by preparative HPLC (Polymer Labs PLRP-S column, 25 x 300 mm, 10  $\mu\text{m}$  particle size, stepwise gradient from 70:30 to 40:60 A:B; A= 90:10:0.2  $\text{H}_2\text{O}$ : MeCN:  $\text{NH}_4\text{OH}$ , B= 90:10:0.2 MeCN: $\text{H}_2\text{O}$ : $\text{NH}_4\text{OH}$ ) and then lyophilized from dioxane- $\text{H}_2\text{O}$  to give the title Compound 355f (0.021 g; 41%) as a white solid (single diastereomer of undetermined configuration).

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m.p. = 68-72°C (dec.);  $[\alpha]_D = -4.0^\circ$  (c = 0.10, MeOH)

55

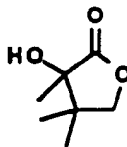
Mass Spec. (FAB):  $(\text{M} + \text{H})^+ = 681$ .



## Exempl 356

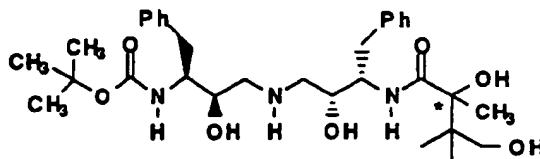
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,4-Dihydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 356b)

## (a) Compound 356a



A solution of  $\text{CH}_3\text{MgCl}$  (3 M in THF, 14.32 mL, 43 mmol) was added to a solution of dihydro-4,4-dimethyl-2,3-furandione (5 g, 39 mmol) in 30 mL THF at  $-78^\circ\text{C}$ . The mixture was allowed to warm to RT, diluted with  $\text{Et}_2\text{O}$  and dilute HCl was added. The organic layer was washed with sat.  $\text{NaHCO}_3$ , dried ( $\text{MgSO}_4$ ) and concentrated to afford 3.5 g of a colorless oil. This material was dissolved in 50 mL THF, and a solution of LiOH (583.4 mg, 24.3 mmol) in 25 mL water was added and the mixture was refluxed for 24 h. The mixture was concentrated, the residue dissolved in 30 mL water, washed with  $\text{Et}_2\text{O}$ , and the aqueous phase lyophilized to afford 3.0 g of a pale solid. This solid (1.0 g) was dissolved in 5 mL water which was acidified with 10% HCl, extracted with  $\text{EtOAc}$ , and the organic phase dried ( $\text{MgSO}_4$ ), concentrated, and the residue purified by flash chromatography (silica gel/hexane-EtOAc 1:1) to afford 0.815 g of Compound 356a as a colorless oil.

## (b) Compound 356b

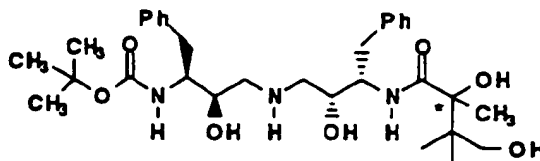


(single isomer at \*)

A mixture of Compound 54 (200 mg, 0.45 mmol) and Compound 356a (129.8 mg, 0.90 mmol) in 1 mL dry DMF was heated at  $100^\circ\text{C}$  for 14 h and  $145^\circ\text{C}$  for 2 h, concentrated, and the residue purified by flash chromatography to afford a ca. 1:1 mixture of the two diastereomeric (at \*) products. This material was subjected to preparative TLC (0.5 mm silica gel plates/ $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$  9:1:0.1, developed twice) to afford, as the faster moving isomer, the title Compound 356b (11 mg, 4.1 %) as a white solid. m.p.  $73-75^\circ\text{C}$ ;  $[\alpha]_D^{25} +8^\circ$  ( $c = 0.15$ , MeOH);  $R_f$  ( $\text{SiO}_2$ ) = 0.23 ( $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$  8:2:0.2). Mass Spec.: 588 ( $\text{M}+\text{H}$ ) $^+$ .

## Example 357

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,4-Dihydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 357)



(single isomer at \*)

Compound 357 (white solid) was isolated as the slower moving isomer by preparative TLC as described in Example 356b.

m.p. 71-75°C,  $R_f$  (SiO<sub>2</sub>) = 0.20 (CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH 8:2:0.2).

5 Mass Spec. 588 (M+H)<sup>+</sup>.

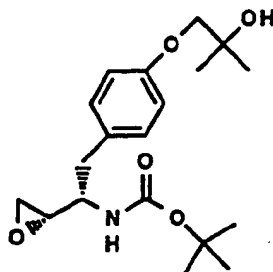
#### Example 358

10 Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxy-2-methylpropoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 358b)

##### (a) Compound 358a

15

20



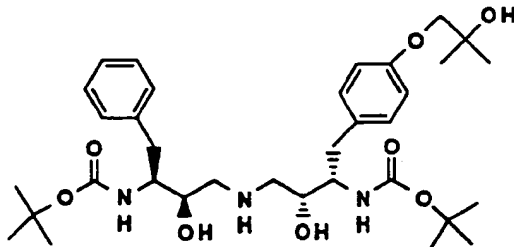
25

Compound 346a was reacted with CH<sub>3</sub>MgBr by a procedure analogous to that of Example 158a to give Compound 358a.

##### (b) Compound 358b

30

35



40

Compounds 358a and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 358b (white solid).

m.p. 85-88°C;  $[\alpha]_D = -4.5^\circ$  (c = 0.11, CH<sub>3</sub>OH)

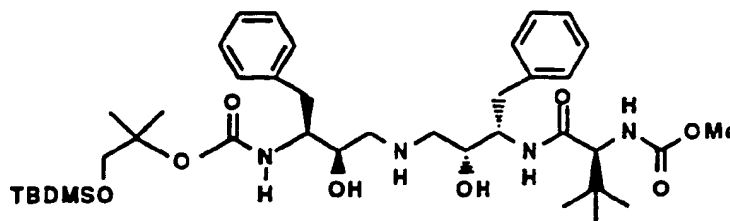
Mass Spec. (FAB): (M+H) = 632.

45

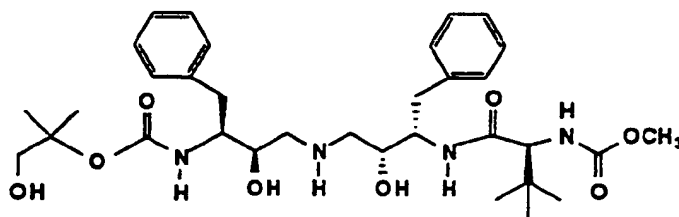
#### Example 359

50 Preparation of [1R\*,2S\*(2S\*,3R\*)]-N-[2-Hydroxy-3-[[[2-hydroxy-3-[[[(2-hydroxy-1,1-dimethylethoxy)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide (Compound 359b)

55

(a) Compound 359a

To a 0°C solution of Compound 246a (0.036 g, 0.191 mmol) in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> was added HOBt-hydrate (0.035 g, 0.261 mmol) followed by EDCI (0.037 g, 0.191 mmol). The mixture was stirred at 0°C for 0.5 h and Compound 333b (0.1 g, 0.174 mL) was added followed by N-methylmorpholine (0.058 mL, 0.522 mmol) and 0.5 mL of DMF. The resulting solution was stirred at RT for 20 h. The mixture was diluted with EtOAc and washed with sat. NaHCO<sub>3</sub> and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue obtained was flash chromatographed on silica gel eluting with a stepwise gradient of 98.9:1:0.1 to 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH to afford Compound 359a (0.096 g, 74%) as a white solid. Mass Spec (FAB) - (M+H)<sup>+</sup> = 745.

(b) Compound 359b

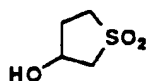
A solution of Compound 359a (0.095 g, 0.127 mmol) in 3 mL of 3:1:1 HOAc-THF-H<sub>2</sub>O was stirred at RT for 16 h. The mixture was concentrated *in vacuo* and flash chromatographed twice on silica gel eluting with a stepwise gradient of 98.9:1:0.1 to 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH-NH<sub>4</sub>OH to obtain a solid which was triturated twice with Et<sub>2</sub>O to afford Compound 359b (0.07 g, 87%) as a white solid. m.p. 93-104°C; [α]<sub>D</sub><sup>20</sup> = -21.2° (c = 0.2, CH<sub>3</sub>OH). Mass Spec. (FAB): (M + H)<sup>+</sup> = 631

Analysis calc. for C <sub>33</sub> H <sub>50</sub> N <sub>4</sub> O <sub>8</sub> · 3.03 H <sub>2</sub> O:			
	C, 57.83;	H, 8.24;	N, 8.18
Found:	C, 57.92;	H, 7.66;	N, 8.09.

	C, 57.83;	H, 8.24;	N, 8.18
Found:	C, 57.92;	H, 7.66;	N, 8.09.

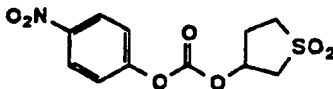
Example 360

Preparation of [1S-(1R\*,2S\*)]-[iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl tetrahydro-1,1-dioxo-3-thienyl ester (Compound 360c)

(a) Compound 360a

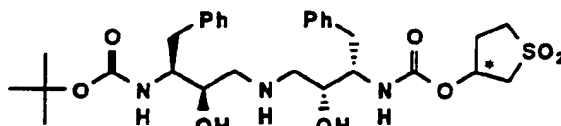
Compound 360a was prepared from tetrahydrothiophene-3-one in two steps employing the procedure described in Dodd et al., *J. Heterocyclic. Chem.*, 27, 1453 (1990).

5 (b) Compound 360b



Compound 360a was converted to Compound 360b by a procedure analogous to that of Example 149d.

15 (c) Compound 360c



(1:1 mixture of isomers at \*)

Compounds 360b and 54 were converted to the title Compound 360c (white solid) in 13% yield by a procedure analogous to that of Example 147d (DMF only used).

m.p. 197-201°C.

Mass Spec. (FAB): 606 (M+H<sup>+</sup>)

Analysis calc. for C<sub>30</sub>H<sub>43</sub>N<sub>3</sub>O<sub>8</sub>S:

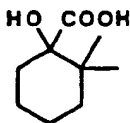
C, 59.49; H, 7.15; N, 6.94; S, 5.29

Found: C, 59.44; H, 7.17; N, 7.07; S, 5.23.

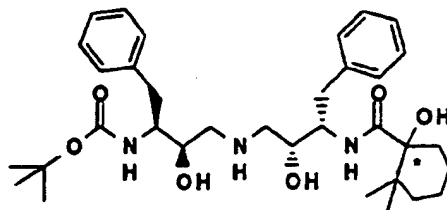
35 Example 361

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3[[3-[[2,2-Dimethyl-1-hydroxycyclohexyl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 361b)

40 (a) Compound 361a



2,2-Dimethylcyclohexanone was converted to Compound 361a by a three-step procedure analogous to that used for the preparation of Compound 321c.

(b) Compound 361b

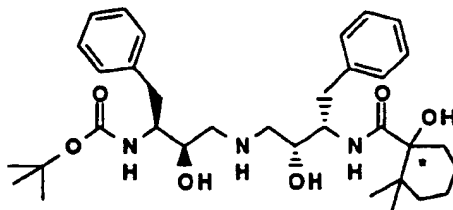
(single isomer of undetermined absolute stereochemistry at \*)

Compounds 361a and 54 were reacted by a procedure analogous to that of Example 321d. The crude product was chromatographed on a 2.5 x 25 cm silica gel column as follows: 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>; 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>; 2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>; 3-4.75% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.3-0.75% NH<sub>4</sub>OH in 0.25% and 0.025% increments respectively. The faster moving isomer was further purified by preparative HPLC (UV 220; YMC S-10 ODS (C-18) 30 x 500 mm column; stepwise gradient from 76-86% MeOH/H<sub>2</sub>O + 0.1% TFA) followed by chromatography on a 2.5 x 5 cm silica gel column using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.5% NH<sub>4</sub>OH to give 59 mg (17%) of the title Compound 361b as a white solid. m.p. 175-180°C; R<sub>f</sub> = 0.20, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection); [α]<sub>D</sub> = +6.2° (C 0.42, MeOH). Mass Spec. CI + ions: M+H = 598.

Analysis calc. for C <sub>34</sub> H <sub>51</sub> N <sub>3</sub> O <sub>6</sub> :			
	C, 68.31;	H, 8.60;	N, 7.03;
Found:	C, 68.38;	H, 8.80;	N, 7.08.

Example 362

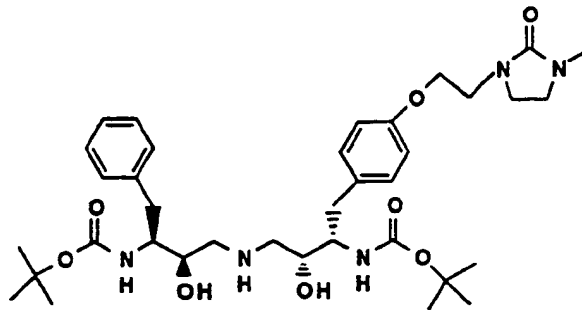
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2,2-Dimethyl-1-hydroxycyclohexyl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 362)



(single isomer of undetermined absolute stereochemistry at \*)

The slower moving isomer of Example 361b was further purified by preparative HPLC (UV 220; YMC S-10 ODS (C-18) 30 x 500 mm column; stepwise gradient from 76-86% MeOH/H<sub>2</sub>O + 0.1% TFA) followed by chromatography on a 2.5 x 5 cm silica gel column using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.5% NH<sub>4</sub>OH to afford 50 mg (15%) of Compound 362 as a white solid. m.p. 101-105°C; R<sub>f</sub> = 0.17, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection); [α]<sub>D</sub> = -4.1° (C 0.49, MeOH). Mass Spec. FAB + ions: M+H = 598.



(d) Compound 363d

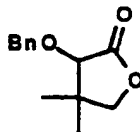
Compounds 363c and 16b were reacted by a procedure analogous to that of Example 226b to give the title Compound 363d as a white solid.

m.p. 63-66°C;  $[\alpha]_D^{25} = +2.5^\circ$  (c 0.12, CH<sub>3</sub>OH)

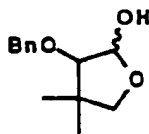
Mass Spec. (FAB): (M+H) = 686

Example 364

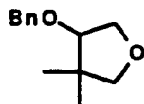
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[tetrahydro-3-hydroxy-4,4-dimethyl-3-furanyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)-propyl]carbamic acid, 1,1-dimethylethyl ester, Isomer A (Compound 364f)

(a) Compound 364a

(D,L)-Pantolactone was converted to Compound 364a by a procedure analogous to that of Example 306a.

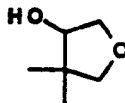
(b) Compound 364b

To a -78°C solution of Compound 364a (7.50 g; 34.0 mmol) in anhydrous toluene and CH<sub>2</sub>Cl<sub>2</sub> (75 mL each) was added a solution of DIBAL-H (40.90 mL of a 1.0 M solution in hexanes; 40.9 mmol) over 1 h. The solution was stirred at -78°C for 2 h. MeOH (9.0 mL) was added dropwise. The resulting suspension was allowed to warm to RT. Brine (31 mL) and Et<sub>2</sub>O (1 L) were added, followed by MgSO<sub>4</sub> (70 g). The suspension was stirred for 1.5 h, and then filtered. The solids were washed with EtOAc and the combined filtrates were concentrated *in vacuo* to give a viscous oil, which solidified on standing to give Compound 364b (7.11 g; 94%; 5.4:1 mixture of anomers) as a white solid.

(c) Compound 364c

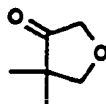
To a -78°C solution of Compound 364b (5.97 g; 26.8 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> were successively added Et<sub>3</sub>SiH (12.84 mL, 80.4 mmol), and BF<sub>3</sub>·OEt<sub>2</sub> (3.63 mL; 29.5 mmol) dropwise. The solution was stirred at -78°C for 2 h, then slowly warmed to 0°C and stirred for 1 h, then cooled to -78°C. NaHCO<sub>3</sub> (9.0 g) was added and the mixture was stirred at -78°C for 15 min. Saturated aq. NaHCO<sub>3</sub> was added, and the mixture was allowed to warm to RT over 1 h. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (MgSO<sub>4</sub>), concentrated *in vacuo*, and purified by flash chromatography (SiO<sub>2</sub>; 200 mL) using a stepwise gradient from 99:1 to 90:10 hexanes:Et<sub>2</sub>O to give Compound 364c (4.89g; 88%) as a colorless oil.

(d) Compound 364d



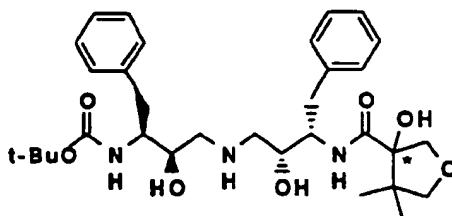
Compound 364c was converted to Compound 364d by a procedure analogous to that described in Example 19.

(e) Compound 364e



Compound 364d was converted to Compound 364e by a procedure analogous to that of Example 314a.

(f) Compound 364f



(single isomer at \*)

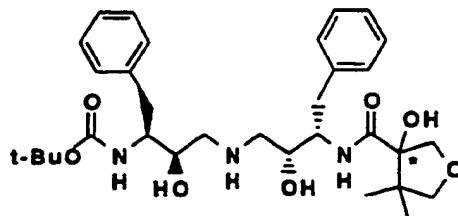
Compounds 364e and 54 were converted to the title Compound 364f by a four-step procedure analogous to that described in Example 321. Flash chromatography (100 mL SiO<sub>2</sub>; stepwise gradient from 99:1:0.1 to 90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) followed by preparative HPLC (Polymer Labs PLRP-S column, 25 x 300 mm, 10 μm particle size, stepwise gradient from 70:30 to 45:55 A:B (where A = 90:10:0.2 H<sub>2</sub>O:MeCN:NH<sub>4</sub>OH and B = 90:10:0.2 MeCN:H<sub>2</sub>O:NH<sub>4</sub>OH)), and lyophilization from dioxane-H<sub>2</sub>O gave 19 mg of Compound 364f as a white solid. m.p. = 84°-87°C; [α] = +6.8° (c = 0.20, MeOH); R<sub>f</sub> (SiO<sub>2</sub>) = 0.29 (90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH). Mass Spec. (CI): (M + H)<sup>+</sup> = 586

Analysis calc. for C <sub>32</sub> H <sub>47</sub> N <sub>3</sub> O <sub>7</sub> ·0.78 H <sub>2</sub> O:			
	C, 64.07;	H, 8.16;	N, 7.01
Found:	C, 63.99;	H, 7.97;	N, 7.09.



## Exempl 365

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[tetrahydro-3-hydroxy-4,4-dimethyl-3-furanyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)-propyl]carbamic acid, 1,1-dimethyl ethyl ester, Isomer B (Compound 365)



(single isomer at \*)

Flash chromatography followed by preparative HPLC as described in Example 364f gave 17 mg of the title Compound 365 (white solid).

m.p. = 82°-85°C;  $[\alpha]_D^{25} = -13.7^\circ$  (c = 0.16, MeOH);  $R_f$  (SiO<sub>2</sub>) = 0.19 (90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH).

Mass Spec. (CI): (M + H)<sup>+</sup> = 586

Analysis calc. for C<sub>32</sub>H<sub>47</sub>N<sub>3</sub>O<sub>7</sub>·0.69 H<sub>2</sub>O:

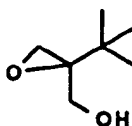
C, 64.25; H, 8.15; N, 7.02

Found: C, 64.24; H, 8.02; N, 7.03.

## Example 366

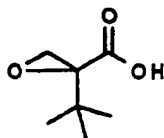
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2-Hydroxy-2-(hydroxymethyl)-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 366d)

## (a) Compound 366a



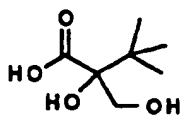
To a solution of 80% m-CPBA (8.5 g, 39.41 mmol) in 160 mL CH<sub>2</sub>Cl<sub>2</sub> was added Compound 262a (3 g, 26.27 mmol) in 30 mL CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and the mixture stirred at RT for 20 h. The reaction mixture was cooled to 0°C and quenched by addition of Me<sub>2</sub>S (6 mL) and washed with 10% aq. Na<sub>2</sub>CO<sub>3</sub>. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layer dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed by distillation. Fractional distillation (10-23 mm, 70-90°C) of the residue afforded Compound 366a (2.63 g, 77% yield) as a light yellow liquid.

## (b) Compound 366b



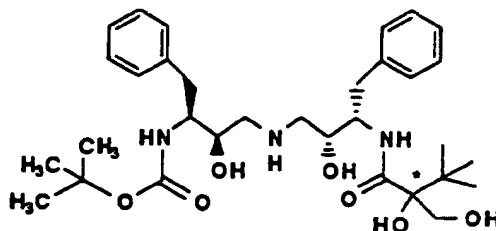
T Compound 366a (2.47 g, 18.97 mmol) in CH<sub>3</sub>CN (65 mL), was added 0.85 mL H<sub>2</sub>O, followed by NaIO<sub>4</sub> (12.17 g, 56.92 mmol) and RuCl<sub>3</sub> (86.5 mg, 0.417 mmol) and the slurry stirred at RT for 2-3 min, after which another 0.85 mL H<sub>2</sub>O was added and the mixture stirred at RT for 2 h. The reaction mixture was diluted with Et<sub>2</sub>O, filtered through celite and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in 1N NaOH (pH ca. 12), extracted with Et<sub>2</sub>O and the aqueous layer separated and acidified (pH 3.0) by addition of 3N HCl. Saturation of the aqueous phase with Na<sub>2</sub>SO<sub>4</sub>, and extraction with EtOAc afforded Compound 366b (1.58 g, 58% yield) as a brown oil.

(c) Compound 366c



To Compound 366b (1.58 g, 10.97 mmol) in H<sub>2</sub>O (55 mL), was added 10% H<sub>2</sub>SO<sub>4</sub> (25 mL) and the mixture heated at 100-105°C for 8 h. The mixture was cooled to RT, saturated with Na<sub>2</sub>SO<sub>4</sub> and extracted with EtOAc. The organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with 80:20:0.2 to 0:100:1 hexane:EtOAc:HOAc to afford Compound 366c (276 mg, 16% yield) as a white solid.

(d) Compound 366d

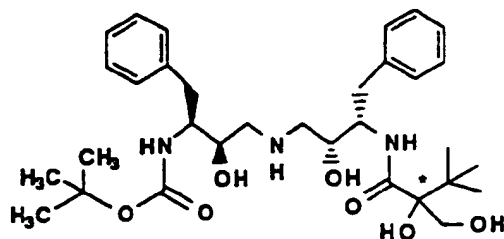


(single isomer at \*)

To a solution of Compound 54 (300 mg, 0.676 mmol) in DMF (1.5 mL) was added a solution of Compound 366c (120 mg, 0.743 mmol) in 0.3 mL DMF, followed by BOP reagent (329 mg, 0.743 mmol) and N-methylmorpholine (164  $\mu$ L, 1.48 mmol) at 0°C. The mixture was heated at 50°C for 24 h, and then stirred at RT for another 24 h. DMF was removed *in vacuo* and the residue dissolved in EtOAc, washed with saturated NaHCO<sub>3</sub> and then with brine. The organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford the crude product as a mixture of diastereomers. Combination with material from a prior reaction (0.113 mmol scale reaction) and chromatography on silica gel, eluting with 99:1:0.1 to 92:8:0.8 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH gave Compound 366d as the faster moving isomer. Further purification by preparative HPLC (Polymer Labs PLRP-S 100 Å, 10  $\mu$  column, stepwise gradient [65:35 C:D to 55:45 C:D (1 h); C = 10% CH<sub>3</sub>CN/ H<sub>2</sub>O + 0.2% aq. NH<sub>4</sub>OH; D = 90% CH<sub>3</sub>CN/ H<sub>2</sub>O + 0.2% aq. NH<sub>4</sub>OH]) gave the title Compound 366d (13 mg, 3%) as a white solid. m.p. 83-85°C; R<sub>f</sub> (SiO<sub>2</sub>) = 0.4 (90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH). Mass spectrum (Fab): (M + H)<sup>+</sup> 588<sup>+</sup>.

Example 367

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2-Hydroxy-2-(hydroxymethyl)-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 367)



(single isomer at \*)

The slower moving isomer from Example 366d was purified by preparative HPLC in analogy to Compound 366d to afford Compound 367 as a white solid.

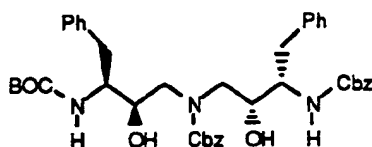
m.p. 84-86°C;  $R_f$  (SiO<sub>2</sub>) = 0.3 (90:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH).

Mass spectrum (Fab): (M + H)<sup>+</sup> 588<sup>+</sup>.

#### Example 368

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,2-Dimethyl-1-hydroxycyclohexyl)-carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester, isomer A (Compound 368f)

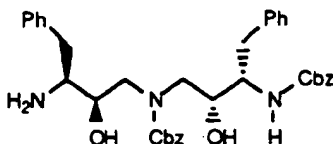
#### (a) Compound 368a



To an ice cooled solution of 1.75 g (3 mmol) of Compound 45 and 1.03 ml (6 mmol) of *i*-Pr<sub>2</sub>NEt in 10 ml of DMF was added dropwise 470  $\mu$ l (3.3 mmoles) of benzyl chloroformate, neat. Stirring was continued with cooling for 0.5 h, then at RT overnight. The solution was evaporated to dryness and the residue purified by flash chromatography on a 1250 cc column of silica gel. Elution with 40% EtOAc - hexane afforded 2.0 g (94%) of Compound 368a as a white solid.

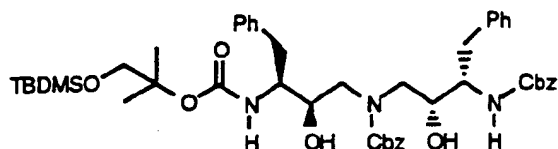
TLC (SiO<sub>2</sub>)  $R_f$  = 0.14 (1:1 EtOAc/Hexane).

#### (b) Compound 368b



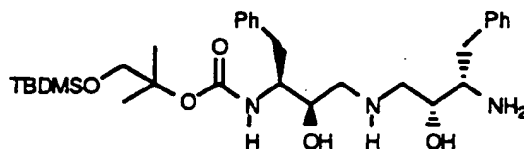
To 1.88 g (2.64 mmol) of Compound 368a at 0°C was added 10 ml of 4 N HCl-dioxane. The reaction was stirred with cooling until solution was obtained, then at RT for an additional 3 h. The reaction mixture was evaporated to dryness and the residue evaporated twice from MeOH to afford 1.54 g (90%) of Compound 368b as a white solid.

TLC (SiO<sub>2</sub>)  $R_f$  = 0.33 (10% MeOH/CHCl<sub>3</sub>).

(c) Compound 368c

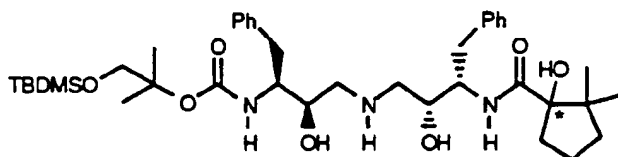
A solution of 1.38 g (2.13 mmol) of Compound 368b, 0.86 g (2.34 mmol) of Compound 161d, and 2.2 ml of  $i\text{-Pr}_2\text{NEt}$  in 10 ml of DMF was stirred at RT for 5 d. The solution was evaporated to dryness and the residue dissolved in EtOAc. The solution was washed with 1 N HCl, brine, 1 N NaOH, and brine and dried ( $\text{MgSO}_4$ ). After removal of solvent, the residue was purified by flash chromatography on a 500 cc column of silica gel. Elution with 25 % EtOAc - hexane, followed by 50 % EtOAc - hexane afforded 1.36 g (76 %) of Compound 368c as a solid white foam.

TLC ( $\text{SiO}_2$ )  $R_f$  = 0.25 (1:1 EtOAc/hexane).

(d) Compound 368d

A solution of 1.0 g (1.19 mmol) of Compound 368c in 20 ml of EtOH was hydrogenated over 100 mg of 20 %  $\text{Pd}(\text{OH})_2/\text{C}$  catalyst for 2 h at RT. To the reaction was added 1 ml of  $\text{NH}_4\text{OH}$  and stirring was continued for 0.5 h. The catalyst was removed by filtration through Celite and the filtrate evaporated to dryness to give 717 mg (100 %) of Compound 368d as a solid foam.

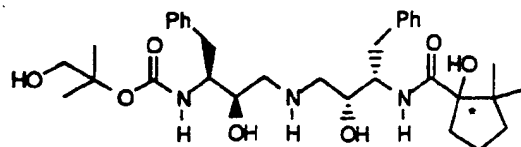
TLC ( $\text{SiO}_2$ )  $R_f$  = 0.21 ( $\text{CHCl}_3$ :MeOH:aq.  $\text{NH}_4\text{OH}$  90:10:1).

(e) Compound 368e

(1:1 mixture of isomers at \*)

To a solution of 700 mg (1.22 mmol) of 368d, 193 mg (1.22 mmol) of Compound 321c, and 148  $\mu\text{l}$  (1.35 mmol) of  $N$ -methylmorpholine in 5 ml of DMF, with ice cooling, was added 597 mg (1.35 mmol) of BOP reagent. Stirring was continued with cooling for 2 h, then at RT overnight. After removal of the DMF (high vac,  $30^\circ\text{C}$ ) the residue, in EtOAc, was washed with brine and dried ( $\text{MgSO}_4$ ). The solvent was removed and the residue purified by flash chromatography on a 125 cc column of silica gel. Elution with  $\text{CHCl}_3$ :MeOH: $\text{NH}_4\text{OH}$  (95:5:0.5) afforded 737 mg (85 %) of Compound 368e as a white foam.

TLC( $\text{SiO}_2$ )  $R_f$  = 0.39 and 0.34 ( $\text{CHCl}_3$ :MeOH:aq. $\text{NH}_4\text{OH}$  90:10:1).

(f) Compound 368f

(single isomer at \*)

A solution of 720 mg (1 mmol) of Compound 368e in 10 ml HOAc:H<sub>2</sub>O:THF (3:1:1) was stirred at RT for 48 h. The reaction was evaporated to dryness and the clear colorless oil residue dissolved in EtOAc and washed with sat. aq. NaHCO<sub>3</sub> and with brine and dried (MgSO<sub>4</sub>). Removal of solvent gave 654 mg of crude material which was purified by flash chromatography on a 125 cc column of silica gel. Elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (95:5:0.5) afforded, as the faster moving isomer, Compound 368f, which was triturated with CHCl<sub>3</sub> to afford 161 mg (0.27 mmole) of the title Compound 368f as a white powder.

m.p. 178-179°C; [α]<sub>D</sub> = + 16.0° (c 0.73, MeOH) R<sub>f</sub> (SiO<sub>2</sub>) = 0.20 (CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH, 90:10:1).

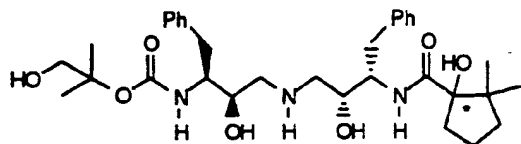
Mass Spec.: (M+H)<sup>+</sup> 600<sup>+</sup>

Analysis calc. for C<sub>33</sub>H<sub>49</sub>N<sub>3</sub>O<sub>7</sub> · 0.85 H<sub>2</sub>O:

	C, 64.45;	H, 8.31;	N, 6.83.
Found:	C, 64.20;	H, 8.09;	N, 7.08.

Example 369

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,2-Dimethyl-1-hydroxycyclopentyl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester, isomer B (Compound 369)



(single isomer at \*)

The slower moving isomer from Example 368f was further purified by preparative HPLC on a YMC S-10 ODS (30x500 mm) column. Gradient elution from 60-90% MeOH-H<sub>2</sub>O + 0.1 % TFA afforded a white foam which was passed through a short column of silica gel (elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH, 90:10:1) to give 71 mg of Compound 369 as a solid white foam.

m.p. 90-100°C (softening at 80°); [α]<sub>D</sub> = - 12.9° (c 0.79, MeOH).

R<sub>f</sub> (SiO<sub>2</sub>) = 0.17 (CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH, 90:10:1).

Mass Spec.: (M+H)<sup>+</sup> 600<sup>+</sup>

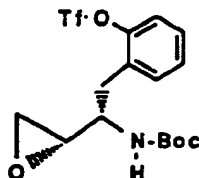
Analysis calc. for C<sub>33</sub>H<sub>49</sub>N<sub>3</sub>O<sub>7</sub> · 0.40 H<sub>2</sub>O:

	C, 65.30;	H, 8.27;	N, 6.92.
Found:	C, 65.39;	H, 8.32;	N, 6.83.

## Example 370

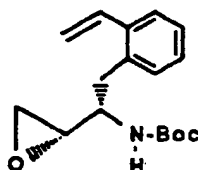
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(2-ethoxyphenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 370c)

## (a) Compound 370a



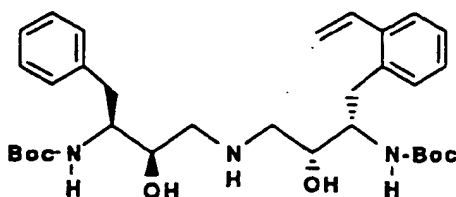
A solution of Compound 349a (1.9 g, 6.8 mmol) in 100 ml of  $\text{CH}_2\text{Cl}_2$  was cooled at  $0^\circ\text{C}$  and N-phenyltriflimide (2.67 g, 7.47 mmol) was added followed by  $\text{Et}_3\text{N}$  (1.15 ml, 8.25 mmol). The reaction was stirred at  $0^\circ\text{C}$  for 2.5 h and then allowed to warm to RT and stir overnight. Additional quantities of N-phenyltriflimide (800 mg, 2.24 mmol) and  $\text{Et}_3\text{N}$  (345 ml, 2.48 mmol) were added. Stirring was continued for an additional 6 h at RT. The reaction was diluted with  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$ , 1 N NaOH,  $\text{H}_2\text{O}$ , and brine. After drying ( $\text{Na}_2\text{SO}_4$ ), the solvents were removed and the crude material was purified on a 250 ml silica column eluting with  $\text{EtOAc}$ /hexanes (1:4) to afford 1.6 g (68%) of Compound 370a as a colorless solid.

## (b) Compound 370b



To a solution of the Compound 370a (610 mg, 1.5 mmol) in 10 ml of 1-methyl-2-pyrrolidinone was added LiCl (190 mg, 4.5 mmol) and triphenylarsine (90 mg, 0.3 mmol) and the reaction mixture was degassed with argon. Tris(dibenzylidene-acetone)dipalladium (0) (138 mg, 0.15 mmol) was added and the mixture stirred for 5 min. Vinyltributyltin (0.520 ml, 560 mg, 1.8 mmol) was added and the reaction mixture was then stirred for 2.5 h at RT and heated at  $55^\circ\text{C}$  overnight. An additional 20% of triphenylarsine (18mg),  $\text{Pd}^0$  (28mg) and vinyltributyltin (104 ml) were added and heating was continued for an additional 6 h. The mixture was poured into 1:1 sat.  $\text{NaHCO}_3/\text{H}_2\text{O}$  and extracted with  $\text{EtOAc}$ . The combined  $\text{EtOAc}$  extract was washed with  $\text{H}_2\text{O}$  and brine and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed and the crude material was purified on a 100 ml silica column eluting with 10 to 20%  $\text{EtOAc}$ /hexane gradient to afford 190 mg (44%) of Compound 370b as a colorless solid.

## (c) Compound 370c



Compounds 370b and 16b were reacted by a procedure analogous to that of Example 304c to afford the title Compound 370c (colorless solid).

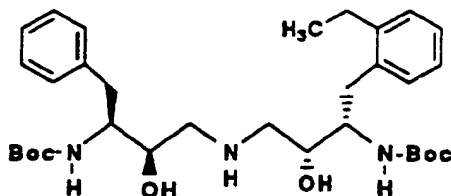
m.p.  $173-176^\circ\text{C}$  (dec);  $[\alpha]_D = -6.0^\circ$  (c 0.5, MeOH)

Mass Spec.: (M+H)<sup>+</sup> 570<sup>+</sup>Analysis calc. for C<sub>32</sub>H<sub>47</sub>N<sub>3</sub>O<sub>8</sub> · 1.5 H<sub>2</sub>O:

	C, 64.40;	H, 8.40;	N, 7.05.
Found:	C, 64.21;	H, 8.03;	N, 7.00.

**Example 371**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(2-ethyl-phenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 371)



A solution of Compound 370c (68 mg, 0.12 mmol) in 3 ml of MeOH containing 7 mg of 10% Pd/C catalyst was stirred under a hydrogen atmosphere (balloon) for 12 h. The reaction was filtered and the MeOH evaporated to afford 66 mg (98%) of Compound 371 as a colorless solid.

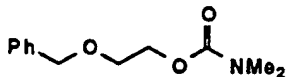
m.p. 178-181°C (dec); [α]<sub>D</sub> = - 5.6° (c 0.5, MeOH)

Mass Spec.: (M+H)<sup>+</sup> 572<sup>+</sup>Analysis calc. for C<sub>32</sub>H<sub>49</sub>N<sub>3</sub>O<sub>8</sub> · 1.75 H<sub>2</sub>O:

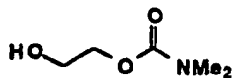
	C, 63.61;	H, 8.91;	N, 7.08.
Found:	C, 63.71;	H, 8.77;	N, 6.97.

**Example 372**

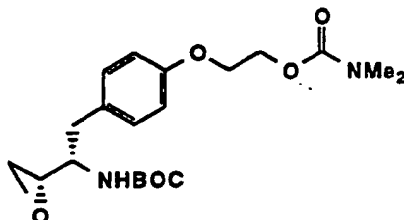
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-3-[[4-[4-[2-[[[(Dimethylamino)carbonyl]oxy]ethoxy]phenyl]-3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxybutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (Compound 372d)

**(a) Compound 372a**

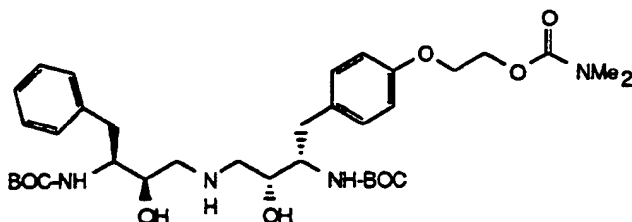
To a stirred solution of phosgene in toluene (8.5 mL of a 1.93 M solution; 16.4 mmol) at -60°C was added a solution of 2-benzyloxyethanol (467 μL, 3.28 mmol) and pyridine (583 μL, 7.22 mmol) in 3 mL CH<sub>2</sub>Cl<sub>2</sub>. After adding 20 mL more CH<sub>2</sub>Cl<sub>2</sub>, the temperature of the reaction mixture was allowed to rise to 15°C and was then cooled to -20°C. Excess N,N-dimethylamine was bubbled through the turbid mixture which was stirred at RT overnight. The solution was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to afford the crude product which was purified by chromatography on a column (5 cm X 15 cm) of silica gel eluting with EtOAc-hexane (20-80 to 25-75) to afford 490 mg (67%) of Compound 372a.

(b) Compound 372b

Compound 372a was converted to Compound 372b by a procedure analogous to that of Example 208 (EtOH was used instead of MeOH).

(c) Compound 372c

Compounds 372b and 175c were converted to Compound 372c by a procedure analogous to that of Example 282a.

(d) Compound 372d

Compounds 372c and 16b were reacted by a procedure analogous to that of Example 304c to give the title Compound 372d (white solid).

m.p. 128-132°C;  $[\alpha]_D = -3.1^\circ$  (c 0.52, MeOH)

Mass Spec. (FAB), 675 (M+H)<sup>+</sup>

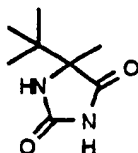
Analysis calc. for C<sub>35</sub>H<sub>54</sub>N<sub>4</sub>O<sub>9</sub> · 0.54 H<sub>2</sub>O:

	C, 61.41;	H, 8.11;	N, 8.18.
Found:	C, 61.40;	H, 7.95;	N, 8.19.

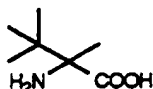
Example 373

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenyl-butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-1,2-dimethylpropyl]carbamic acid, methyl ester, isomer A (Compound 373d)

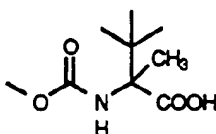


(a) Compound 373a

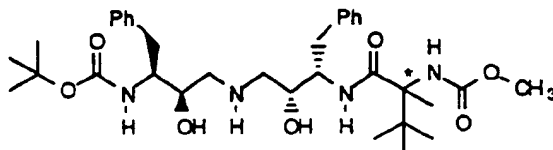
Compound 373a was prepared as described in Obrecht et al., *Helv. Chim. Acta*, 75, 1666 (1992).

(b) Compound 373b

A solution of 1.2 g (7.1 mmol) of 373a in 25 ml of concentrated HCl was heated at 130°C, in a pressure vessel, for 7 d. After cooling to RT, the solution was evaporated to dryness to yield a solid residue which was taken into H<sub>2</sub>O, washed with CH<sub>2</sub>Cl<sub>2</sub>, and again evaporated to dryness to yield 1.6 g of Compound 373b as a tan solid.

(c) Compound 373c

Compound 373b was converted to Compound 373c by a procedure analogous to that of Example 246a.

(d) Compound 373d

(single isomer at \*)

Compounds 373c and 54 were converted to the title Compound 373d by a two-step procedure analogous to that employed for the synthesis of Compound 312d (CH<sub>2</sub>Cl<sub>2</sub> only used for reaction of HOBT with Compound 373c). The crude product was purified by flash chromatography on a 45 cc column of silica gel. Elution with CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH (95:5:0.5) afforded 140 mg of a mixture of isomers which were separated by preparative HPLC on a YMC S-10 ODS (30x500 mm) column. Isocratic elution with 70 % MeOH-H<sub>2</sub>O + 0.1 % TFA, gave as the faster moving isomer on C-18. Compound 373d, which was passed through a short column of silica gel (elution with CHCl<sub>3</sub>:MeOH: NH<sub>4</sub>OH (90:10:1)) and triturated with Et<sub>2</sub>O to afford 42 mg (16%) of the title Compound 373d as a white solid.

m.p. 120-122°C; [α]<sub>D</sub> = - 0.9° (c 0.66, MeOH)

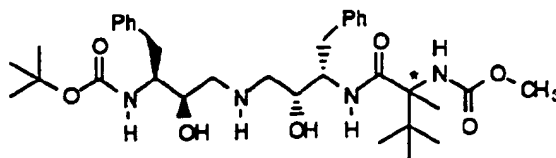
Mass Spec.: (M+H)<sup>+</sup> 629<sup>+</sup>

Analysis calc. for  $C_{34}H_{52}N_4O_7$ :

	C, 64.94;	H, 8.33;	N, 8.91.
Found:	C, 64.54;	H, 8.13;	N, 8.57.

**Example 374**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-1,2-dimethylpropyl]carbamic acid, methyl ester, isomer B (Compound 374)



(single isomer at \*)

The slower moving isomer on C-18 was isolated by preparative HPLC as described in Example 373d followed by passage through a short column of silica gel (elution with  $CHCl_3$ :MeOH:  $NH_4OH$  (90:10:1)) and trituration with  $Et_2O$  to afford 54 mg (20%) of Compound 374 as a white solid.

m.p. 168-170°C;  $[\alpha]_D = -21.5^\circ$  (c 0.75, MeOH)

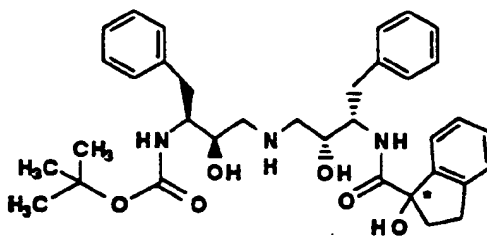
Mass Spec.:  $(M+H)^+$  629<sup>+</sup>

Analysis calc. for  $C_{34}H_{52}N_4O_7$ :

	C, 64.94;	H, 8.33;	N, 8.91.
Found:	C, 64.75;	H, 8.33;	N, 8.68.

**Example 375**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,3-Dihydro-1-hydroxy-1H-inden-1-yl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 375)



(single isomer at \*)

1-Indanone was converted to a 1:1 mixture of Compounds 375 and 376 by a four-step procedure analogous to that used for the synthesis of Compounds 321 and 322. Compound 375 (white solid) was isolated as the faster moving isomer by silica gel chromatography, eluting with 99:1:0.1 to 94:6:0.6  $CH_2Cl_2$ : $CH_3OH$ :aq.  $NH_4OH$ .

m.p. 189-192°C;  $[\alpha]_D = -15.7^\circ$  (c 0.2,  $CH_3OH$ )

$R_f$  ( $SiO_2$ ) = 0.32 (99:1:0.1  $CH_2Cl_2$ : $CH_3OH$ :aq.  $NH_4OH$ )

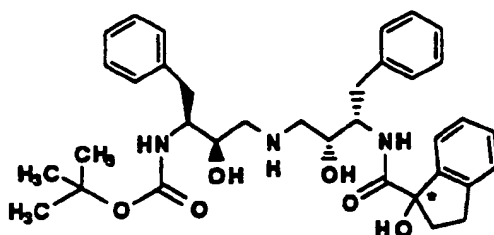
Mass Spec. (Fab):  $(M+H)^+$  604.

Analysis calc. for  $C_{35}H_{45}N_3O_8$ :

	C, 69.63;	H, 7.51;	N, 6.96.
Found:	C, 69.28;	H, 7.51;	N, 6.97.

**Example 376**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(2,3-Dihydro-1-hydroxy-1H-inden-1-yl)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 376)

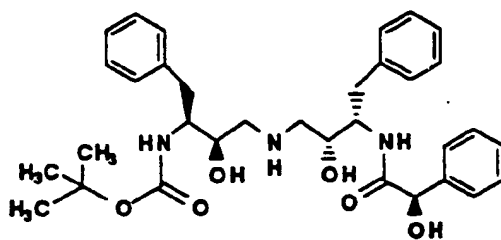


(single isomer at \*)

Compound 376 (white solid) was isolated as the slower moving isomer as described in Example 375.  
 m.p. 100-102°C;  $[\alpha]_D = +15.0^\circ$  (c 0.22, CH<sub>3</sub>OH)  
 $R_f$  (SiO<sub>2</sub>) = 0.25 (99:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH)  
 Mass Spec. (Fab): (M + H)<sup>+</sup> 604.

**Example 377**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[3-[2-Hydroxy-1-oxo-2-phenylethyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 377)

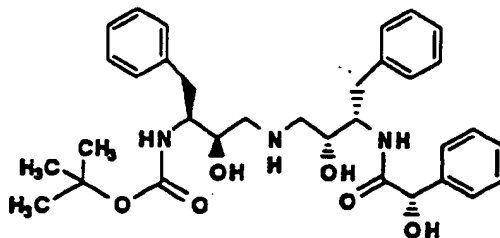


To a solution of (R)-mandelic acid (100 mg, 0.225 mmol) in DMF (0.5 mL) was added Compound 54 (37.6 mg, 0.247 mmol), followed by BOP reagent (241 mg, 0.545 mmol) and N-methylmorpholine (132  $\mu$ L, 1.20 mmol) at 0°C. The mixture was stirred at RT for 16 h. DMF was removed *in vacuo* and the residue dissolved in EtOAC, washed with saturated aq. NaHCO<sub>3</sub> and then with brine. The organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* and the residue purified by silica gel chromatography, eluting with 99:1:0.1 to 91.5:8.5:0.85 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH to afford Compound 377 (94 mg, 72%) as a white solid.  
 m.p. 125-127°C;  $[\alpha]_D = -13.0^\circ$  (c 0.2, CH<sub>3</sub>OH)  
 Mass Spec. (Fab): (M + H)<sup>+</sup> 578.

Analysis calc. for: C <sub>33</sub> H <sub>43</sub> N <sub>3</sub> O <sub>6</sub> · 0.80 H <sub>2</sub> O			
	C, 66.93;	H, 7.59;	N, 7.10.
Found:	C, 66.76;	H, 7.55;	N, 7.27.

**Example 378**

Preparation of [1S-[1R\*,2S\*[2S\*,3R\*(R\*)]]-[3-[[3-[2-Hydroxy-1-oxo-2-phenylethyl)amino]-2-hydroxy-4-phenylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester (Compound 378)



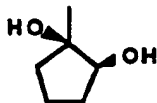
(S)-Mandelic acid and Compound 54 were reacted by a procedure analogous to that of Example 377 to afford the title Compound 378 (white solid).  
 m.p. 135-138°C;  $[\alpha]_D^{25} = +9.1^\circ$  (c 0.22, CH<sub>3</sub>OH)  
 Mass Spec. (Fab): (M + H)<sup>+</sup> 578<sup>+</sup>.

Analysis calc. for: C<sub>33</sub>H<sub>43</sub>N<sub>3</sub>O<sub>6</sub> · 0.63 H<sub>2</sub>O  
 C, 67.28; H, 7.57; N, 7.13.  
 Found: C, 67.12; H, 7.54; N, 7.29.

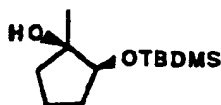
**Example 379**

Preparation of [1S-(1R\*,2S\*) (trans)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 1,1-dimethylethyl 2-hydroxy-1-methylcyclopentyl ester (Compound 379e)

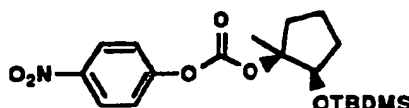
(a) Compound 379a



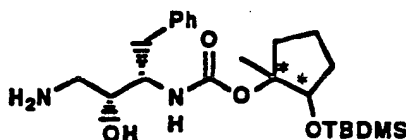
A solution of NaOH (600 mg; 15 mmol) and KMnO<sub>4</sub> (2.81 g; 17.8 mmol) in 95 ml of H<sub>2</sub>O precooled to 0°C was added to a slurry of 1-methylcyclopentene (1 g; 12 mmol), t-BuOH (120 ml), H<sub>2</sub>O (25 ml) and ice (60 g) at -10°C. The resulting mixture was stirred 10 min at -10°C. Sodium sulfite (2.3 g) was added and the mixture was filtered through celite. The filtrate was concentrated to ~30 ml by distillation of the solvents at atmospheric pressure. Solid NaCl was added to saturation and the mixture was extracted with EtOAc. After drying (MgSO<sub>4</sub>), the organic layer was concentrated to afford 1.03 g (74%) of racemic Compound 379a.

(b) Compound 379b

Compound 379a was converted into racemic Compound 379b by a procedure analogous to that of Example 264b.

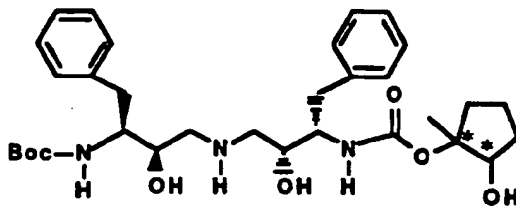
(c) Compound 379c

Compound 379b was converted into racemic Compound 379c by a procedure analogous to that of Example 161d.

(d) Compound 379d

(1:1 mixture of isomers at \*; S,R:R,S)

Compounds 379c and 298a were reacted by a two-step procedure analogous to that used for the conversion of Compound 282c to Compound 282e to afford Compound 379d.

(e) Compound 379e

(1:1 mixture of isomers at \*; S,R:R,S)

Compounds 379d and 1b(i) were reacted by a two-step procedure analogous to that used for the conversion of Compound 282e to Compound 282g to afford the title Compound 379e (white solid).  
m.p. 102-113°C (\*shrinkage at 68-87°C);

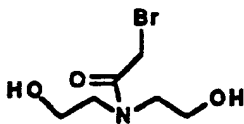
Mass Spec.(FAB) (M + H)<sup>+</sup> = 586

Analysis calc. for C<sub>32</sub>H<sub>46</sub>N<sub>3</sub>O<sub>7</sub>·0.98H<sub>2</sub>O:

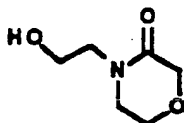
	C, 63.81;	H, 8.02;	N, 6.98
Found:	C, 63.81;	H, 8.17;	N, 6.98.

**Example 380**

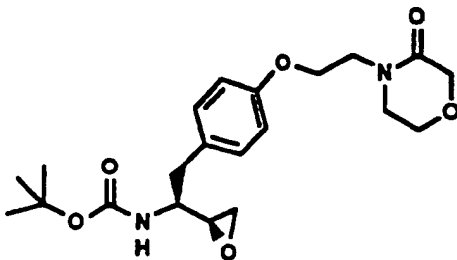
Preparation of [1S-[1R\*, 2S\*(2S\*,3R\*)]]-3-[[3-[[[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(3-oxo-4-morpholinyl)ethoxy]phenyl]-butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid, 1,1-dimethyl-1,1-dimethyl ester (Compound 380d)

**(a) Compound 380a**

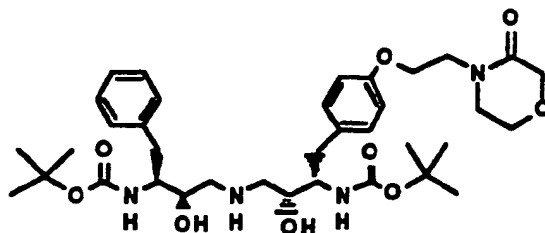
To a 0°C solution of diethanolamine (2.10 g; 20.0 mmol) in 40 mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added dry Et<sub>3</sub>N (4.2 mL; 30.0 mmol) and bromoacetyl bromide (2.1 mL; 24.0 mmol). The reaction mixture was stirred at 5°C for 3 h, then at RT overnight. Volatiles were removed *in vacuo* and the residue was purified on silica using 100% EtOAc to afford 1.5 g of pure Compound 380a (33%).

**(b) Compound 380b**

To a suspension of NaH (260 mg; 6.63 mmol; 60% in mineral oil) in 1.0 mL of dry DMF at 0°C was added a solution of Compound 380a (1.5 g; 6.63 mmol) in 5.5 mL of dry DMF. The solution was allowed to warm to RT. After 6 h another 260 mg (6.63 mmol) of NaH was added and the mixture was stirred overnight. The reaction was quenched with H<sub>2</sub>O and concentrated *in vacuo* to give crude material which was purified on silica gel using a stepwise gradient from 2% to 8% MeOH:CH<sub>2</sub>Cl<sub>2</sub>:0.1% NH<sub>4</sub>OH to afford Compound 380b (600 mg; 62%).

**(c) Compound 380c**

Compounds 175c and 380b were reacted by a procedure analogous to that of Example 282a to give Compound 380c.

(d) Compound 380d

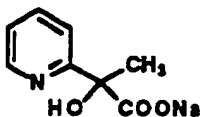
Compounds 16b and 380c were reacted by a procedure analogous to that of 304c to give the title Compound 380d (white solid).

m.p. 108-111°C;  $[\alpha]_D = -3.3^\circ$  (c 0.03, CH<sub>3</sub>OH)

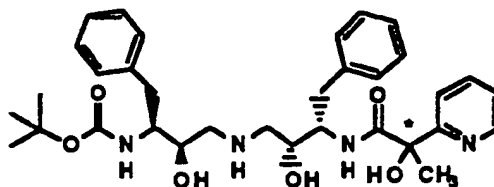
Mass Spec. (FAB): (M+H) = 687.

Example 381

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-hydroxy-1-oxo-2-(2-pyridinyl)propyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 381b)

(a) Compound 381a

ZnI<sub>2</sub> (96 mg; 0.3 mmol) was added to a solution of 2-acetylpyridine (1.10 ml; 9.8 mmol) and trimethylsilylcyanide (1.70 ml; 12.7 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> at 20°C. After stirring at RT for 3 h, the solvent was removed *in vacuo* and the residue was stirred in ~4 ml of concentrated HCl at RT for 40 h. After cooling to 0°C, the pH of the reaction mixture was adjusted to 9 with 6 N NaOH. The basic mixture was washed with EtOAc, concentrated to ~15 ml and loaded onto an HP-20 column, eluting with water, to afford 940 mg (50%) of Compound 381a as a white solid.

(b) Compound 381b

(single isomer at \*)

Compounds 54 and 381a were reacted by a procedure analogous to that described in Example 321d to afford a 1:1 mixture of Compounds 381b and 382. The diastereomers were separated by preparative HPLC [YMC S-10 ODS (C-18) 30 x 500 mm column; stepwise gradient from 56-74% MeOH/H<sub>2</sub>O + 0.1% TFA]. Final isolation of the faster moving isomer by chromatography on a 2.5 x 10 cm silica gel column using 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> + 0.5% NH<sub>4</sub>OH as the mobile phase gave 88 mg (33%) of the title Compound 381b as a white solid.

m.p. 114-117°C. (s fms at 92°C);  $R_f$  (SiO<sub>2</sub>) = 0.25, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection);  $[\alpha]_D = -7.8$  (c 0.32, MeOH).

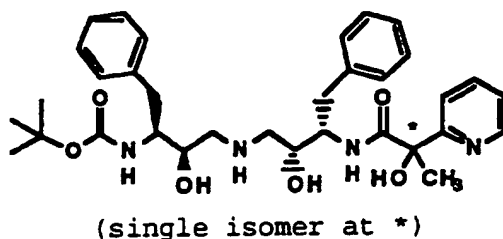
Mass Spec. FAB: M+H = 593.

Analysis calc. for  $C_{33}H_{44}N_4O_6 \cdot 0.49 H_2O$ :

	C, 65.90;	H, 7.54;	N, 9.31;
Found:	C, 66.10;	H, 7.45;	N, 9.11.

**Example 382**

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-hydroxy-1-oxo-2-(2-pyridinyl)propyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 382)



Compound 382 (white solid) was isolated as the slower moving isomer by preparative HPLC followed by silica gel chromatography as described in Example 381b.

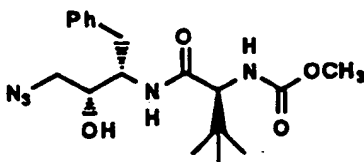
m.p. 92-96°C;  $R_f$  (SiO<sub>2</sub>) = 0.06, CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH, 90:9:1 (UV and PMA detection);  $[\alpha]_D = -5.7^\circ$  (c 0.30, MeOH). Mass Spec. FAB: M+H= 593.

Analysis calc. for  $C_{33}H_{44}N_4O_6 \cdot 0.26 H_2O$ :

	C, 66.34;	H, 7.51;	N, 9.38;
Found:	C, 66.46;	H, 7.65;	N, 9.26.

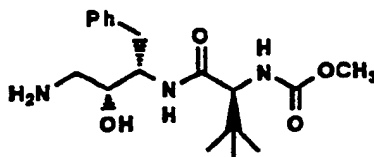
**Example 383**

Preparation of [1R\*,2S\*[2S\*,3R\*(S\*)]]-N-[2-Hydroxy-3-[[2-hydroxy-3-[(2-hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide (Compound 383e)

**(a) Compound 383a**

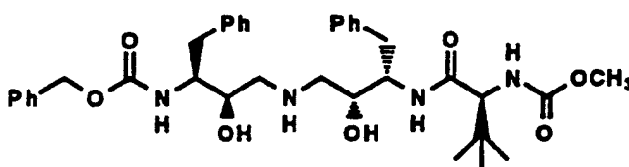
To a solution of Compound 298a (500 mg, 2.42 mmol) in 0.5 mL DMF was added Compound 246a (505 mg, 2.66 mmol), followed by HOBt hydrate (360 mg, 2.66 mmol), N-methylmorpholine (318 mg, 3.15 mmol) and EDCI hydrochloride (510 mg, 2.66 mmol) at 0°C, and the mixture stirred at RT for 21 h. DMF was removed in *vacuo* and the residue dissolved in EtOAc, washed with sat. NaHCO<sub>3</sub> and then brine. The organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated to yield a residue which was purified by silica gel chromatography, eluting from 99.5:0.5:0.05 to 96.5:3.5:0.35 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH to afford Compound 383a (604 mg, 66%) as a white solid. TLC (SiO<sub>2</sub>),  $R_f$  = 0.41 (9:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH - Rydon).



(b) Compound 383b

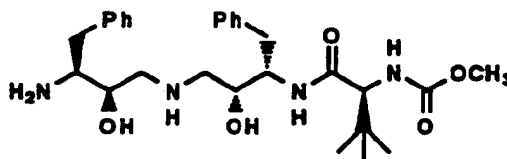
To Compound 383a (604 mg, 1.60 mmol) in THF (7 mL) and H<sub>2</sub>O (43  $\mu$ L) was added Ph<sub>3</sub>P (462 mg, 1.76 mmol) and the solution stirred at RT for 18 h. The solvent was removed *in vacuo* and the resulting residue purified by flash chromatography on silica gel, eluting with a step wise gradient from 99:1:0.1 to 87:13:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH to afford Compound 383b (478 mg, 85%) as a white solid.

TLC (SiO<sub>2</sub>) R<sub>f</sub> = 0.15 (9:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH - Rydon).

(c) Compound 383c

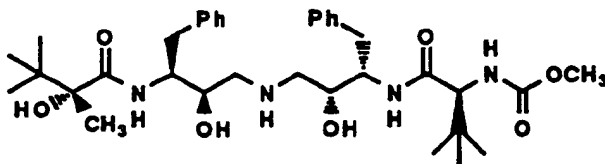
To a solution of Compound 383b (468 mg, 1.33 mmol) in DMF (0.6 mL) was added Compound 44a (396 mg, 1.33 mmol) and the mixture heated at 100°C for 7 h. DMF was removed *in vacuo* and the residue purified by flash chromatography on silica gel, eluting with a step wise gradient from 99:1:0.1 to 82:12:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH to afford Compound 383c (377 mg, 43%) as a white solid.

TLC (SiO<sub>2</sub>) R<sub>f</sub> = 0.28 (9:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH / Rydon).

(d) Compound 383d

To a solution of Compound 383c (366 mg, 0.564 mmol) in EtOH (12 mL) and EtOAc (4 mL) was added 20% Pd(OH)<sub>2</sub>/C (108 mg) and the slurry stirred under a H<sub>2</sub>(g) atmosphere for 18 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with a step wise gradient from 97.5:2.5:0.25 to 87:13:1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH to afford Compound 383d (209 mg, 76%) as a white solid.

TLC (SiO<sub>2</sub>) R<sub>f</sub> = 0.14 (9:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH:aq. NH<sub>4</sub>OH / Rydon).

(e) Compound 383e

To a solution of Compound 383d (105 mg, 0.204 mmol) in DMF (0.5 mL) was added Compound 262e (34.5 mg, 0.236 mmol), followed by BOP reagent (104 mg, 0.236 mmol) and N-methylmorpholine (52  $\mu$ L, 0.473 mmol) and the mixture stirred at RT for 18 h. DMF was removed *in vacuo*, the residue dissolved in EtOAc and washed

with sat.  $\text{NaHCO}_3$  and then brine. The organic layer was separated, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. Purification was achieved by flash chromatography on silica gel, eluting with a step wise gradient from 97.5:2.5:0.25 to 87:13:1  $\text{CH}_2\text{Cl}_2$ : $\text{CH}_3\text{OH}$ :aq.  $\text{NH}_4\text{OH}$  to afford the title Compound 383e (70 mg, 54% yield) as a white solid.

m.p. 94–96°C;  $[\alpha]_D^{25} = +4.54^\circ$  (c 0.22,  $\text{CH}_3\text{OH}$ )

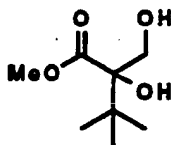
Mass Spec. (Fab):  $(\text{M} + \text{H})^+ 643^+$ .

Analysis calcd. for $\text{C}_{35}\text{H}_{64}\text{N}_4\text{O}_7 \cdot 1.00 \text{ H}_2\text{O}$			
	C, 63.62;	H, 8.54;	N, 8.72.
Found:	C, 63.70;	H, 8.43;	N, 8.40.

#### Example 384

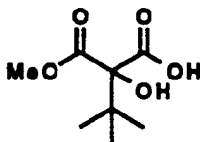
Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[2-Hydroxy-3,3-dimethyl-2-[(methylamino)carbonyl]-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A (Compound 384d)

##### (a) Compound 384a



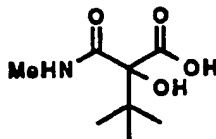
Diazomethane in  $\text{Et}_2\text{O}$  (prepared from 5.45 g of 1-methyl-3-nitro-1-nitrosoguanidine as described in Example 1a(i)) was added to a suspension of Compound 366c (3.0 g, 18.5 mmol) in 50 mL of  $\text{Et}_2\text{O}$  at 0°C. The resulting mixture was quenched with few drops of HOAc and concentrated *in vacuo* to afford Compound 384a (oil; 3.26 g, 100% crude yield).

##### (b) Compound 384b

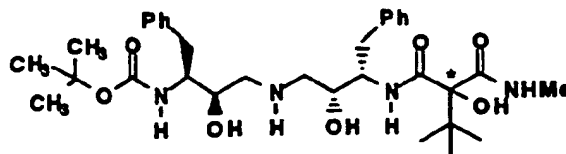


Compound 384a was converted to Compound 384b by a two-step procedure analogous to that used for the synthesis of Compound 262e.

##### (c) Compound 384c



A mixture of methylamine (ca. 5 g) and Compound 384b (0.9 g, 4.74 mmol) in 10 mL of MeOH was heated in a sealed tube at 150°C for 3 h and concentrated *in vacuo*. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with 20% aq. sulfuric acid, the combined aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic phase was dried ( $\text{MgSO}_4$ ) and concentrated to afford the Compound 384c (0.55 g, 61%) as a colorless oil.

(d) Compound 384d

(single isomer at \*)

Compounds 384c and 54 were converted to the title Compound 384d and its diastereomer Compound 385 by a two-step procedure analogous to that employed for the synthesis of Compound 312d ( $\text{CH}_2\text{Cl}_2$  only was used for the reaction of HOBT with Compound 384c). The mixture was purified by flash chromatography (silica gel/ $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$  99:1:0.1 to 95:5:0.5) to afford 115 mg of a 1:1 mixture of diastereomers which were separated by preparative HPLC (column: Polymer Labs. PLRP-S 100 Å 10  $\mu\text{m}$  25X300 mm; eluent: 30:70 step wise to 1:1 A:B, eluent A =  $\text{H}_2\text{O}$ - $\text{CH}_3\text{CN}$ - $\text{NH}_4\text{OH}$  90:10:0.2, eluent B =  $\text{H}_2\text{O}$ - $\text{CH}_3\text{CN}$ - $\text{NH}_4\text{OH}$  10:90:0.2) to afford the title Compound 384d (faster moving isomer on polymer column) as a white solid (25 mg, 9% yield).

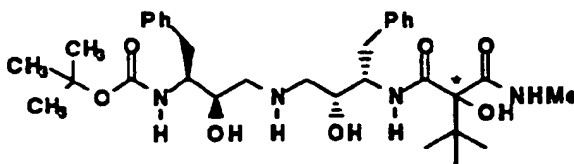
$R_f$  = 0.37 (silica gel/ $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$  9:1:0.1), m.p. 77-78°C,  $[\alpha]_D = -7.5^\circ$  (c 0.6 MeOH).  
Mass Spec.: 615 (M+H)<sup>+</sup>.

Analysis calcd for  $\text{C}_{33}\text{H}_{50}\text{N}_4\text{O}_7 \cdot 0.77 \text{ H}_2\text{O}$ :

	C, 63.05;	H, 8.26;	N, 8.91.
Found:	C, 63.24;	H, 8.17;	N, 8.91.

Example 385

Preparation of [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[2-Hydroxy-3,3-dimethyl-2-[(methylamino)carbonyl]-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B (Compound 385)



(single isomer at \*)

Compound 385 (white solid) was isolated (slower moving isomer on polymer column) by preparative HPLC as described in Example 384d.

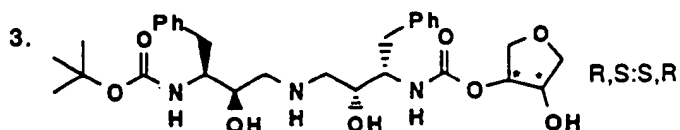
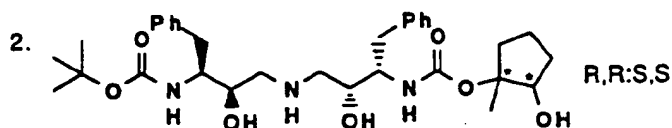
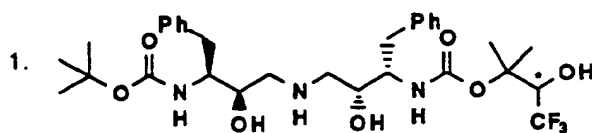
$R_f$  = 0.37 (silica gel/ $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_4\text{OH}$  9:1:0.1), m.p. 76-77°C;  $[\alpha]_D = -15.1^\circ$  (c 0.55 MeOH).

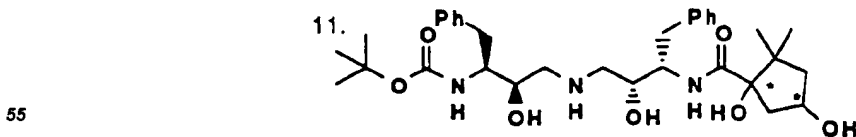
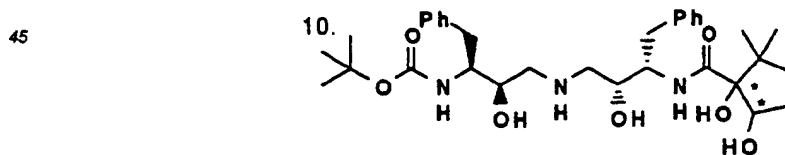
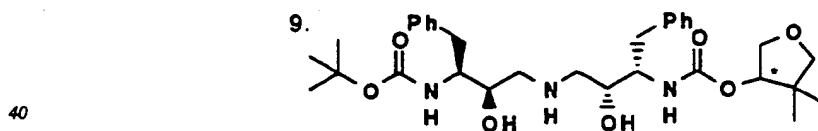
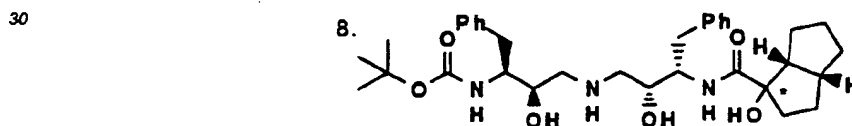
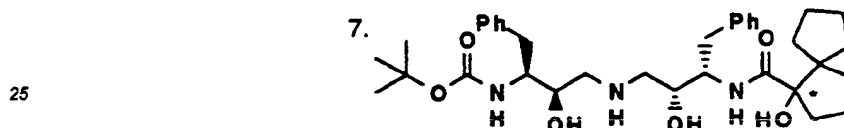
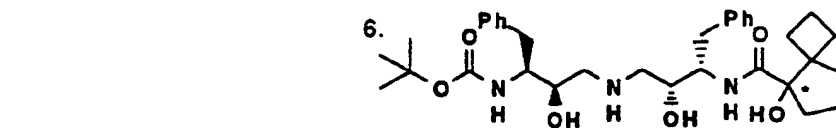
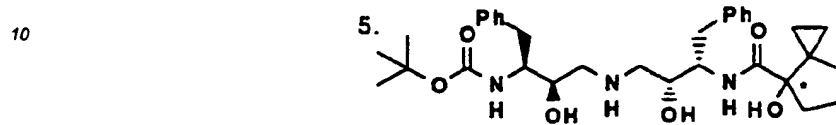
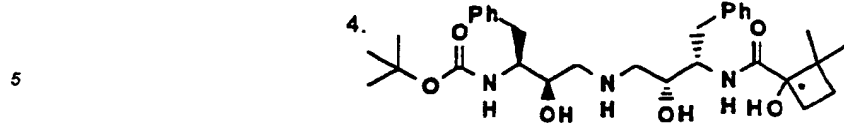
Mass Spec.: 615 (M+H)<sup>+</sup>.

Other compounds contemplated by the present invention include the following compounds:

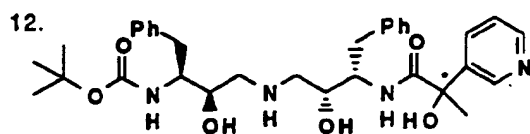
1. [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl 3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl ester.
2. [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl (R,R,S,S)-2-hydroxy-1-methylcyclopentyl ester.
3. [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl (R,S,S,R)-tetrahydro-4-hydroxy-3-furanyl ester.
4. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[1-hydroxy-2,2-dimethylcyclobutyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
5. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[4-hydroxyspiro[2.4]hept-4-yl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.

6. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[5-hydroxyspiro[3.4]oct-5-yl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
7. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[6-hydroxyspiro[4.4]non-6-yl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
8. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[octahydro-1-hydroxy-1-pental-yl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
9. [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl tetrahydro-4,4-dimethyl-3-furanyl ester.
10. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[1,5-dihydroxy-2,2-dimethylcyclopentyl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
11. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[1,4-dihydroxy-2,2-dimethylcyclopentyl)carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
12. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-hydroxy-1-oxo-2-(3-pyridinyl)-propyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
13. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2,3,3-trimethyl-2-[(methylamino)-carbonyl]-1-oxobutyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
14. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-cyano-2,3,3-trimethyl-1-oxobutyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
15. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[2-cyano-3,3-dimethyl-1-oxobutyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
16. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[[4-hydroxy-2-[(methoxycarbonyl)amino]-3,3-dimethyl-1-oxobutyl]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
17. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[2-(hydroxymethyl)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
18. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[2-(2-hydroxyethyl)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
19. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[2-(3-hydroxypropyl)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
20. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[(4-morpholinylcarbonyl)oxy]methyl]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
21. [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[3-(4-morpholinyl)-3-oxopropyl]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester.
- The above compounds correspond (by number) to the following structures:

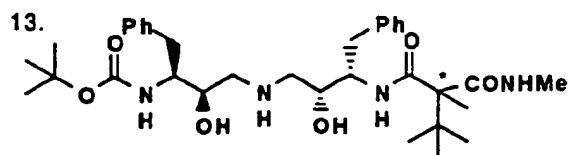




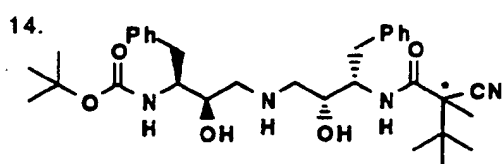
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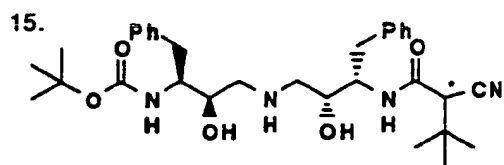


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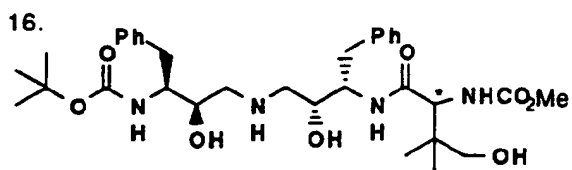
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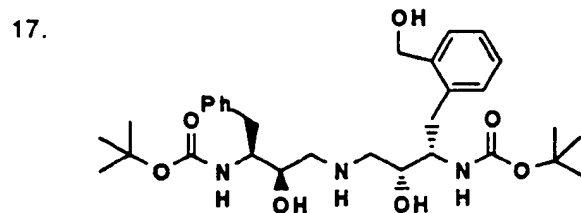
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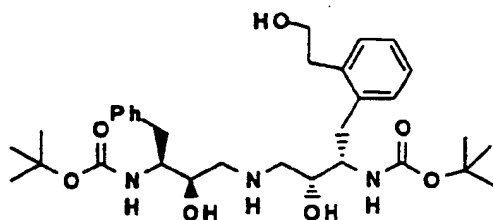
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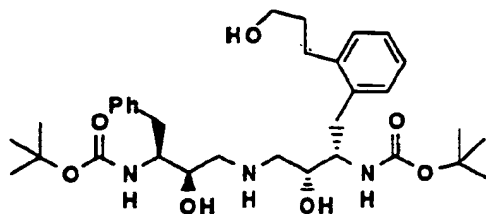
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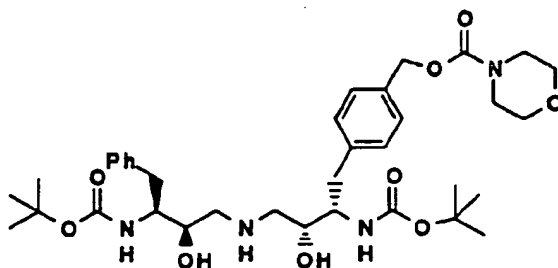
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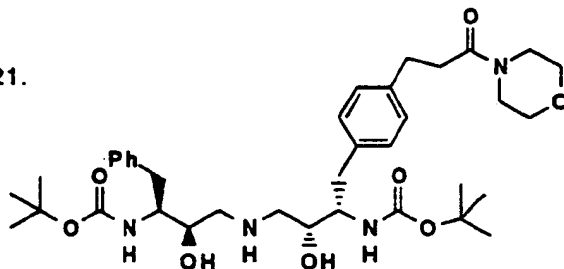
19.



20.



21.



#### HIV Protease Assay

An HIV protease standard assay was performed in a 60  $\mu$ l reaction medium containing 50 mM sodium acetate, pH 5.5, 100  $\mu$ g/ml bovine serum albumen, 450  $\mu$ M substrate ( $H_2N$ -Val-Ser-Gln-Asn-( $\beta$ -naphthyl-alanine)-Pro-Val-Ile-OH), and purified protease. The reaction medium was incubated for 30 minutes at 37°C, quenched by the addition of 140  $\mu$ l 5%  $H_3PO_4$ , then analyzed by reverse phase HPLC using UV<sub>220</sub> detection. In a typical control assay, 7% of the substrate was hydrolyzed. Aminediol inhibitors of the present invention, listed in the following Table 1, were then employed in the assay, for which purpose they were prepared as a 0.5 mM solution in DMSO, then diluted to 30  $\mu$ M with 50 mM sodium acetate/bovine serum albumen. This working stock was then diluted 3-fold into the protease reaction medium, for a final concentration of 10  $\mu$ M inhibitor and 4% DMSO. The results obtained from the assay are shown in the following Table 1.

Cell Culture Anti-HIV Activity

5 The antiviral activity of aminediol inhibitors of the present invention was evaluated by a microculture method which determines the increase in cell viability of an infected culture when a drug is added. The assay depends on the metabolic reduction of tetrazolium reagent by viable cells to yield a soluble colored formazan product.

10 The assay was performed as follows: suspensions of CEM-SS cells (5000/well) were infected with the RF strain of HIV at a multiplicity of infection at 0.04 in a 96-well plate. The compounds of the present invention listed in the following Table 1, serially diluted in half-log fashion, were added to the infected and uninfected control cells. Untreated (infected and uninfected) cells were included as controls. Following incubation for 6 days at 37°C, viable cells in each well were quantitated by the visible light absorbance at 450 nm.

15 The IC<sub>50</sub> was calculated as the concentration of drug that increased the formazan production in virally infected cells to 50% of that produced by uninfected cells in the absence of drug. The results obtained in the assay are shown in the following Table 1.

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Table 1

		HIV Protease	HIV (CEM Cells)
	<u>Compound</u>	<u>% Inhibition at 10<math>\mu</math>M</u>	<u>IC<sub>50</sub> (<math>\mu</math>M)</u>
5	2	100	0.09
10	3	0	>3.2
	5	41	2.8
	7	8	ND
	8	2	ND
15	10	1	ND
	11	0	>6
	12	1	ND
20	13	45	5.3
	14	100	1.1
	15	98	0.38
	16	83	$\geq 2.3$
25	17	84	>1.5
	21	99	0.09
	22	90	>1.8
30	23	98	0.45
	24	78	4.5
	25	98	0.53
35	26i	57	ND
	26ii	41	ND
	27	19	ND
	28	100	0.09
40	29	100	0.1
	30	97	0.5
	31	100	0.03
45	34	20	>9
	36	36	>8
	38	3	>4
	42	100	0.6
50	43	21	ND
	44	58	>5
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	45	87	0.5
5	47	81	1.1
	50	97	0.22
	52	100	0.2
	53	99	0.54
10	55	91	0.7
	56	47	ND
	57	46	ND
15	58	57	1.0
	59	45	ND
	60	78	1.2
	62	98	0.05
20	63	53	ND
	64	72	>5
	65	11	ND
25	66	99	0.27
	67	100	0.04
	68	99	0.11
30	69	11	ND
	70	100	0.5
	71	58	1.2
	72	51>	3.2
35	73	99	0.6
	75	100	5.0
	76	100	0.6
40	77	99	0.2
	78	99	0.16
	79	99	0.4
	80	98	0.3
45	82	94	>3
	83	19	ND
	84	99	1.2
50	86	78	1.8
	87	92	>0.88

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	88	100	0.03
	89	23	ND
5	92	100	39
	93	100	0.18
	94	80-99	ND
10	96	100	>7.6
	98	100	1.3
	99	99	>100
15	100	99	0.23
	101	99	0.14
	102	47	ND
	103	98	1.7
20	104	99	0.03
	105	99	1.6
	106	71	ND
25	112	100	>8.6
	115	58	ND
	117	14	ND
	119	10	ND
30	121	73	>0.3
	123	65	1.0
	125	71	>1.5
35	127	15	ND
	132	65	>3
	134	87	>5
40	136	73	ND
	137	92	>2.6
	138	98	>0.8
	139	73	ND
45	140	61	ND
	141	77	>2.3
	142	30	ND
50	144	88	1.0
	145	95	>2.2

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	146	98	≥3.0
	148	88	2.0
5	150	93	>4.0
	153	65	>0.55
	154	96	>1.2
10	155	95	>0.2
	156	85	>6.0
	157	90	ND
	158	97	>1.8
15	159	100	1.3
	160	99	0.08
	164	99	0.04
20	165	100	0.62
	166	89	1.7
	167	97	>1.8
25	168	61	1.4
	169	97	0.2
	170	100	0.1
	171	99	0.05
30	175	99	0.03
	178	99	0.03
	179	99	0.17
35	180	73	ND
	181	46	ND
	182	41	ND
	183	35	ND
40	184	99	1.3
	185	5	ND
	186	0	ND
45	187	28	ND
	188	21	ND
	189	23	ND
50	190	<16	ND
	191	13	ND

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	192	85	ND
	193	66	ND
5	194	0	>5.0
	195	0	ND
	196	6	ND
10	197	10	>10
	198	10	>14
	199	3	>17
	200	5	>15
15	201	99	0.04
	202	95	16
	203	98	0.2
20	204	99	0.17
	205	98	0.07
	209	99	0.03
25	210	81	>5
	211	99	0.9
	212	99	3.8
	213	98	0.17
30	214	97	0.05
	215	66	ND
	216	49	ND
35	217	100	0.48
	218	96	1.6
	219	86	35
	220	100	0.77
40	221	96	1.1
	222	98	0.38
	223	89	1.4
45	224	98	0.04
	225	99	0.5
	226	98	0.05
50	227	99	0.9
	228	98	0.7

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	229	82	0.6
5	230	92	4.9
	231	83	ND
	232	99	0.05
10	233	100	1.0
	234	100	0.08
	235	97	0.35
	236	89	0.7
15	237	54	ND
	238	64	2.3
	239	37	ND
20	240	99	2.0
	241	95	0.28
	242	99	0.11
	243	99	0.08
25	244	100	1.5
	245	100	1.8
	246	100	0.04
30	247	99	0.1
	248	99	0.23
	249	100	0.84
35	250	100	1.5
	251	98	ND
	252	99	0.06
	253	85	ND
40	254	98	17
	255	86	ND
	256	88	1.5
45	257	99	0.03
	258	91	1.5
	259	99	5.0
50	260	100	0.29
	261	94	1.1
	262	100	0.03
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	263	98	0.34
	264	99	0.16
5	265	100	2.6
	266	69	ND
	267	97	0.18
10	268	94	ND
	269	61	ND
	270	27	ND
	271	99	0.06
15	272	87	ND
	273	100	1.7
	274	99	ND
20	275	95	0.45
	276	97	0.13
	277	67	ND
	278	94	0.84
25	279	54	ND
	280	100	0.05
	281	100	0.29
30	282	100	0.06
	283	100	0.11
	284	100	4.4
35	285	100	0.65
	286	99	5.0
	287	89	ND
	288	100	0.47
40	289	53	ND
	290	99	0.06
	291	73	ND
45	292	99	0.17
	293	99	0.03
	294	89	ND
	295	82	ND
50	296	37	ND

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	297	100	0.05
5	298	100	0.06
	299	99	0.24
	300	99	0.03
	301	95	2.4
10	302	99	0.25
	303	98	0.07
	304	99	0.03
15	305	100	0.2
	306	100	0.06
	308	100	0.02
	309	100	1.8
20	310	100	0.18
	311	100	0.05
	312	95	3.5
25	313	65	ND
	314	100	0.12
	315	100	1.6
30	316	97	0.62
	317	85	ND
	318	100	0.1
	319	93	1.37
35	320	100	0.22
	321	100	0.2
	322	100	0.02
40	323	100	0.014
	324	100	0.22
	325	90	1.54
	326	99	0.03
45	327	99	0.05
	328	99	0.54
	329	84	ND
50	330	92	0.85
	331	99	0.06
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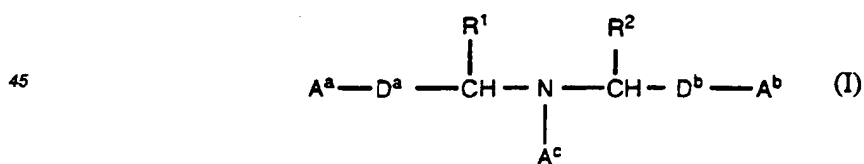
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5	333	100	0.15
	334	99	0.05
	335	89	ND
	336	100	0.04
10	337	99	0.29
	338	99	0.93
	339	99	0.012
15	340	56	ND
	341	99	2.1
	342	99	0.07
	343	99	0.05
20	344	99	0.03
	345	99	0.33
	346	98	>50
25	347	99	0.05
	348	99	ND
	349	98	0.37
30	350	98	0.5
	351	99	0.08
	352	99	0.1
	353	98	1.1
35	354	99	0.12
	355	99	0.07
	356	99	0.12
40	357	99	0.11
	358	99	0.1
	359	99	0.56
45	360	96	0.45
	361	97	ND
	362	98	ND
	363	99	0.04
50	364	98	0.22
	365	72	ND
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	366	99	0.009
5	367	50	ND
	368	98	0.017
	369	96	ND
	370	96	ND
10	371	98	ND
	372	98	ND
	373	85	ND
15	374	28	ND
	375	98	ND
	376	63	ND
	377	95	ND
20	378	27	ND
	379	98	ND
	380	97	ND
25	381	60	ND
	382	89	ND
	383	99	ND
	384	99	ND
30	385	99	ND

ND = Not Determined

# Claims

- 40 1. A compound of the following formula I:



50 where

A<sup>a</sup>, A<sup>b</sup> and A<sup>c</sup> are independently:

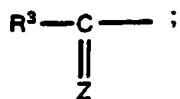
(1) hydrogen;

(2) alkyl;

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(3)

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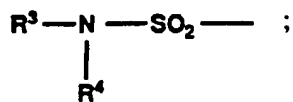


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(4)  $\text{R}^3\text{-SO}_2\text{---}$ ;

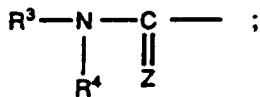
(5)

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(6)

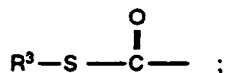
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(7)

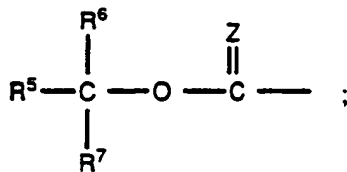
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(8)

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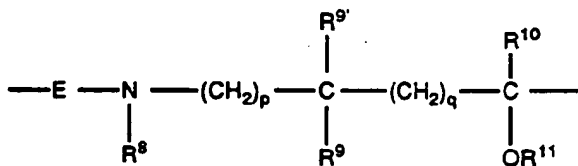


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or

(9)  $\text{R}^3\text{-SO-}$  $\text{D}^a$  and  $\text{D}^b$  are independently selected from groups of the formula:

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where  $\text{D}^a$  and  $\text{D}^b$  are bonded to the groups  $\text{A}^a$  and  $\text{A}^b$ , respectively, through the moiety  $\text{---E-N(R}^8\text{)---}$ , where E is a single bond or a peptide chain containing 1 to 4 amino acids, the N-terminus of which is bonded to  $\text{A}^a$  when E is part of  $\text{D}^a$  or to  $\text{A}^b$  when E is part of  $\text{D}^b$ ;  $\text{R}^1$  and  $\text{R}^2$  are independently:

- (1) hydrogen;
- (2) alkyl;
- (3) alkenyl;
- (4) aryl;
- (5) heterocyclo; or
- (6) carbocyclo;

R<sup>3</sup> and R<sup>4</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) aryl;
- (d) heterocyclo;
- (e) carbocyclo;
- (f) when R<sup>3</sup> and R<sup>4</sup> are bonded to a common nitrogen atom, R<sup>3</sup> and R<sup>4</sup> may be joined, together with that nitrogen atom, to form a heterocyclic ring system; or
- (g) when E is a single bond and R<sup>3</sup> is part of A<sup>a</sup> or A<sup>b</sup>, R<sup>3</sup> may, together with R<sup>6</sup>, form an alkylene group;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) aryl;
- (d) carbocyclo;
- (e) fluorenyl;
- (f) heterocyclo;
- (g) R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> may, independently, be joined, together with the carbon atom to which they are bonded, to form a mono-, bi- or tricyclic carbocyclic ring system, or a mono-, bi- or tricyclic heterocyclic ring system;
- (h) alkynyl;
- (i) alkenyl; or
- (j) when E is a single bond and R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are part of A<sup>a</sup> or A<sup>b</sup>, one of R<sup>5</sup>, R<sup>6</sup>, or R<sup>7</sup> may, together with R<sup>8</sup>, form an alkylene group;

R<sup>8</sup> is:

- (a) hydrogen;
- (b) alkyl;
- (c) R<sup>8</sup> and R<sup>9</sup> may be joined, together with the atoms to which they are bonded, to form a heterocyclic ring system;
- (d) R<sup>8</sup> may be joined together with R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> as described above;
- (e) R<sup>8</sup> may be joined together with R<sup>3</sup> as described above; or
- (f) R<sup>8</sup> and R<sup>11</sup> may be joined, together with the atoms to which they are bonded, to form a heterocyclic ring system;

R<sup>9</sup> and R<sup>9</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) alkenyl;
- (d) alkynyl;
- (e) aryl;
- (f) heterocyclo;
- (g) carbocyclo;
- (h) R<sup>9</sup> may be joined together with R<sup>8</sup> as described above; or
- (i) R<sup>9</sup> and R<sup>9</sup> may be joined, together with the carbon atom to which they are bonded, to form a carbocyclic group;

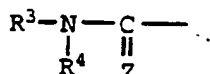
R<sup>10</sup> is:

- (a) hydrogen;
- (b) alkyl;
- (c) alkenyl;
- (d) alkynyl;
- (e) carbocyclo;
- (f) aryl; or
- (g) R<sup>10</sup> and R<sup>11</sup> taken together may form a bond to give a keto group;

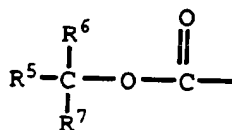
R<sup>11</sup> is:

- (a) hydrogen;  
 (b) a hydroxyl protecting group;  
 (c) R<sup>11</sup> may be joined together with R<sup>8</sup> as described above; or  
 (d) R<sup>11</sup> may, together with R<sup>10</sup>, form a bond to give a keto group as described above;  
 Z is oxygen or sulfur; and  
 p and q are, independently, integers from 0 to 4;  
 or such a compound in salt form.

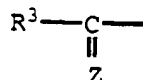
2. A compound of claim 1, wherein A<sup>a</sup> and A<sup>b</sup> are, independently:  
 (A) hydrogen;  
 (B) alkyl;  
 (C) the group:



- where Z is sulfur or oxygen;  
 R<sup>3</sup> is alkyl; and  
 R<sup>4</sup> is hydrogen or alkyl;  
 (D) the group:



- where  
 R<sup>5</sup> is hydrogen; carbocyclo; alkyl; aryl; heterocyclo; or alkynyl;  
 R<sup>6</sup> and R<sup>7</sup> are preferably hydrogen or alkyl; or two of R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup>, together with the carbon atom to which they are bonded, form a carbocyclo group or a heterocyclo group;  
 (E) the group:



- where  
 Z is sulfur or oxygen;  
 R<sup>3</sup> is hydrogen; aryl; alkyl; carbocyclo; or heterocyclo; or  
 (F) the groups:

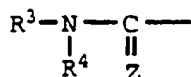


or



where R<sup>3</sup> is alkyl.

3. A compound of claim 2, wherein A<sup>a</sup> and A<sup>b</sup> are, independently:  
 (C) the group:

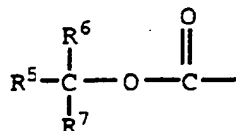


where Z is oxygen;

R<sup>3</sup> is unsubstituted lower alkyl, arylalkyl, or heterocycloalkyl; and

R<sup>4</sup> is hydrogen;

(D) the group:



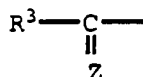
where

R<sup>5</sup> is hydrogen, alkyl, aryl or heterocyclo;

R<sup>6</sup> and R<sup>7</sup> are hydrogen or unsubstituted lower alkyl or hydroxyalkyl; or

two of R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup>, together with the carbon atom to which they are bonded, form a carbocyclo group or a heterocyclo group; or

(E) the group:



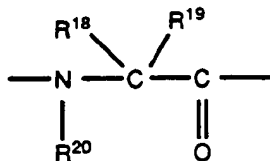
where

Z is oxygen;

R<sup>3</sup> is carbocyclo or alkyl wherein said carbocyclo or alkyl is substituted by one or more of hydroxy, aryl, heterocyclo, alkylaminocarbonyl or fluoro.

4. A compound of any preceding claim, wherein E is a single bond or a peptide chain containing 1 or 2 amino acids.

5. A compound of claim 4, wherein E is a single bond; or a peptide chain containing 1 or 2 amino acids, wherein said amino acids have a structure of the following formula:



where

R<sup>18</sup> is hydrogen or unsubstituted lower alkyl;

R<sup>19</sup> is hydrogen, aryl or lower alkyl; or

R<sup>18</sup> and R<sup>19</sup>, together with the carbon atom to which they are bonded, form a cycloalkyl group; and

R<sup>20</sup> is hydrogen or unsubstituted lower alkyl.

6. A compound of any preceding claim, wherein R<sup>8</sup> is hydrogen; alkyl; R<sup>8</sup> and R<sup>9</sup>, together with the atoms to which these groups are bonded, form a heterocyclo group; R<sup>8</sup> and R<sup>11</sup>, together with the atoms to which these groups are bonded, form a heterocyclo group; or R<sup>8</sup> and A<sup>a</sup> or A<sup>b</sup>, as described above, together with the atoms to which these groups are bonded, form a heterocyclo group.

7. A compound of claim 6, wherein R<sup>8</sup> is hydrogen.

8. A compound of any preceding claim, wherein p and q are zero.

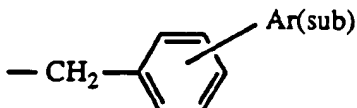
9. A compound of any preceding claim, wherein R<sup>9</sup> is alkyl, hydrogen, aryl, alkenyl, carbocyclo, or R<sup>9</sup> and

R<sup>8</sup>, together with the atoms to which these groups are bonded, form a heterocyclic group.

10. A compound of claim 9, wherein R<sup>9</sup> is unsubstituted lower alkyl, or substituted lower alkyl, wherein said substituted lower alkyl is selected from the group consisting of:

- (A) cycloalkyl-lower alkyl;  
(B) heterocyclo-lower alkyl;  
(C) arylalkenyl-lower alkyl; or  
(D) aryl-lower alkyl.

11. A compound of claim 10, wherein R<sup>9</sup> is aryl-lower alkyl which has the structure of the following formula:



where Ar(sub) is:

- (i) hydrogen;  
(ii) hydroxy;  
(iii) alkenyl;  
(iv) unsubstituted lower alkyl; or  
(v) alkoxy.

12. A compound of claim 11, wherein, when Ar(sub) is an alkoxy group, said alkoxy group is selected from the group consisting of: unsubstituted lower alkoxy; alkoxyalkoxy; hydroxyalkoxy; arylalkoxy; heterocycloalkoxy; aminoalkoxy or aminocarbonyloxyalkoxy where the amino moiety is unsubstituted or mono- or disubstituted by alkyl or aryl; heterocyclocarbonylalkoxy; heterocycloalkoxyalkoxy; alkoxyalkoxy; or carboxyalkoxy.

13. A compound of any preceding claim, wherein R<sup>9</sup> is hydrogen.

14. A compound of any preceding claim, wherein R<sup>10</sup> is hydrogen, arylalkyl, unsubstituted lower alkyl, or R<sup>10</sup> and R<sup>11</sup> together form a keto group.

15. A compound of claim 14, wherein R<sup>10</sup> is hydrogen.

16. A compound of any preceding claim, wherein R<sup>11</sup> is hydrogen; alkoxyalkyl; unsubstituted lower alkyl; R<sup>11</sup> and R<sup>8</sup>, together with the atoms to which these groups are bonded, form a heterocyclic group; or R<sup>11</sup> and R<sup>10</sup> together form a keto group.

17. A compound of claim 16, wherein R<sup>11</sup> is hydrogen.

18. A compound of any preceding claim, wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen or arylalkyl.

19. A compound of claim 18, wherein R<sup>1</sup> and R<sup>2</sup> are hydrogen.

20. A compound of claim 1, which compound is selected from

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-(4-hydroxyphenyl)butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[[methyl(2-pyridinylmethyl)amino]carbonyl]-L-valinamide;

[S-[1R\*,2S\*(2S\*,3R\*)]]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[(1H-benzimidazol-2-ylmethoxy)carbonyl]-L-valinamide;

[1R\*,2S\*(2S\*(2S\*,3R\*))]-N-[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>[(1H-indol-2-ylmethoxy)carbonyl]-L-valinamide;

[R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]biscarbamic acid, 1,1-dimethylethyl-2-hydroxy-1,1-dimethylethyl ester;

5 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

10 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-hydroxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-(2-methoxyethoxy)phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

15 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(4-morpholinyl)-2-oxo-ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[3,3-Dimethyl-2-(formylamino)-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide;

20 [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-benzoxazolyl)methyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[3-[(2-Hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

25 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-1-(phenylmethyl)-3-[[2-hydroxy-4-phenyl-3-[(3,3,3-trifluoro-2-hydroxy-1-oxopropyl)amino]butyl]amino]propyl]carbamic acid, 1,1-dimethylethyl ester (isomer A);

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester;

30 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[2-hydroxy-1-oxo-2-(trifluoromethyl)propyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethylester (isomer A);

[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide;

35 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[2-Hydroxy-3-[[2-hydroxy-3-[(2-hydroxy-1,1-dimethylethoxy)carbonyl]amino]-4-phenylbutyl]amino]-1-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]propyl]carbamic acid, 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(3-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;

40 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[1-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-2-(hydroxymethyl)-2-methylpropyl]carbamic acid, phenylmethyl ester, isomer A;

[S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]aminocarbonyl]propyl]carbamic acid, (2-quinoxaliny)methyl ester;

45 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[3-[[2,2-Dimethyl-1-hydroxycyclopentyl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer B;

[1R\*,2S\*(2S\*,3R\*)]-N-[3-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-2-hydroxy-4-[4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(methoxycarbonyl)-3-methyl-L-valinamide;

50 [1S-[1R\*,2S\*(3R\*)]]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 3-tetrahydrofuranyl 1,1-dimethylethyl ester;

[1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[3-[(2-Hydroxy-2,3,3-trimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester;

55 [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[3-[(2-Hydroxy-3,3-dimethyl-1-oxobutyl)amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethyl ester;

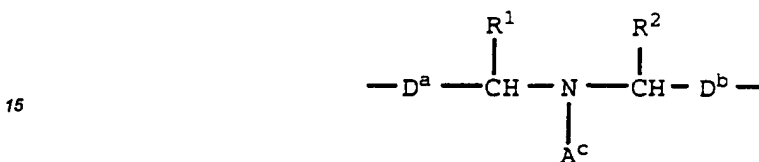
N, N'-[Imin bis[(1S,2R)-2-Hydroxy-1-(Phenylmethyl)-3,1-propanediyl]]bis-[1-hydroxy-2,2-dimethylcyclopentanecarboxamide], isomer A;

[S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[3-[[3-[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-



- 4-ph nylbutyl]amino]-2-hydroxy-1-(phenylm thyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-furo [2,3-c]pyridinyl) methyl ster;  
 [2R-[R\*(R\*,S\*)]]-N,N'-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[2-hydroxy-2,3,3-trimethylbutaneamide];  
 [S-[1R\*,2S\*(2S\*,3R\*)]]-[2,2-Dimethyl-1-[[[3-[[[1,1-dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]propyl]carbamic acid, (2-furo [2,3-b]pyridinyl)methyl ester;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-[4-[2-hydroxy-2-(3-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2,4-Dihydroxy-2,3,3-trimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A;  
 [1R\*,2S\*(2S\*,3R\*)]-N-[2-Hydroxy-3-[[2-hydroxy-3-[[[2-hydroxy-1,1-dimethylethoxy]carbonyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2-Hydroxy-2-(hydroxymethyl)-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2,2-Dimethyl-1-hydroxycyclopentyl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester, isomer A;  
 [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[[2-Hydroxy-1-oxo-2-phenylethyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester; and  
 [1R\*,2S\*(2S\*,3R\*(S\*))]-N-[2-Hydroxy-3-[[2-hydroxy-3-[[[2-hydroxy-2,3,3-trimethyl-1-oxobutyl]amino]-4-phenylbutyl]amino]-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide; and stereoisomers and pharmaceutically acceptable salts thereof.
21. A compound of claim 20, wherein said compound is selected from  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 [R-(R\*,S\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]biscarbamic acid, 1,1-dimethylethyl-2-hydroxy-1,1-dimethylethyl ester;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-(4-[2-(4-morpholinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-(4-[2-(2-pyridinyl)ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-(4-[2-(4-morpholinyl)-2-oxo-ethoxy]phenyl]butyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 [1R\*,2S\*(2S\*,3R\*)]-N-[3-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-N<sup>2</sup>-(2-methoxycarbonyl)-3-methyl-L-valinamide;  
 [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[[2-Hydroxy-2,3,3-trimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 [1S-(1R\*,2S\*,3R\*)]-[Iminobis[2-hydroxy-1-(phenylmethyl)-3,1-propanediyl]]bis[carbamic acid], 3-tetrahydrofuranyl 1,1-dimethylethyl ester;  
 [1S-[1R\*,2S\*(2S\*,3R\*(S\*))]]-[3-[[[2-Hydroxy-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester;  
 N, N'-[Iminobis[(1S,2R)-2-Hydroxy-1-(Phenylmethyl)-3,1-propanediyl]]bis-[1-hydroxy-2,2-dimethylcyclopentanecarboxamide], isomer A;  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2-Hydroxy-2-(hydroxymethyl)-3,3-dimethyl-1-oxobutyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 1,1-dimethylethyl ester, isomer A; and  
 [1S-[1R\*,2S\*(2S\*,3R\*)]]-[3-[[[2,2-Dimethyl-1-hydroxycyclopentyl]carbonyl]amino]-2-hydroxy-4-phenylbutyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid, 2-hydroxy-1,1-dimethylethyl ester, isomer A;  
 and pharmaceutically acceptable salts thereof.
22. Use of a compound of any preceding claim for the manufacture of a medicament for treatment of conditions which require inhibition of HIV protease.

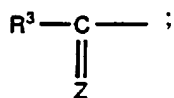
23. Use according to claim 22, wherein, simultaneously or sequentially, a compound selected from the following compounds is also administered in said treatment: HIV protease inhibitors other than those of claim 1, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors; inhibitors of *tat*; CD<sub>4</sub> receptor viral binding inhibitors; inhibitors of RNase, integrase, or *rev*; and immunomodulators.
24. A pharmaceutical composition for the inhibition of HIV protease, comprising a compound of any one of claims 1-21 in amount effective therefor, and a pharmaceutically acceptable vehicle or diluent.
25. A compound which is capable of inhibiting HIV protease, wherein said compound contains the moiety:



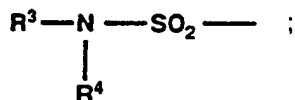
where

A<sup>c</sup> is:

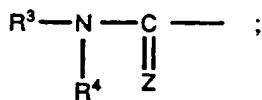
- (1) hydrogen;  
(2) alkyl;  
(3)



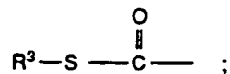
- (4) R<sup>3</sup>-SO<sub>2</sub>-;  
(5)



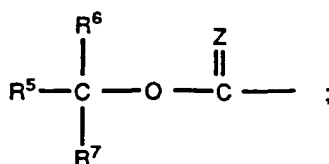
(6)



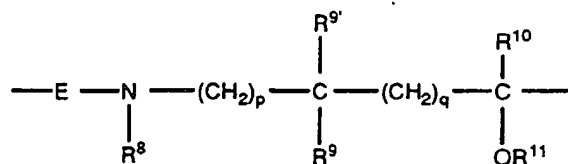
(7)



(8)



or

(9) R<sup>3</sup>-SO-D<sup>a</sup> and D<sup>b</sup> are independently selected from groups of the formula:

where D<sup>a</sup> and D<sup>b</sup> are bonded to the groups -CH(R<sup>1</sup>)- and -CH(R<sup>2</sup>)-, respectively, through the moiety -C(R<sup>10</sup>)(OR<sup>11</sup>)-, where E is a single bond or a peptide chain containing 1 to 4 amino acids, the C-terminus of which is bonded to -N(R<sup>8</sup>)-;

R<sup>1</sup> and R<sup>2</sup> are independently:

- (1) hydrogen;
- (2) alkyl;
- (3) alkenyl;
- (4) aryl;
- (5) heterocyclo; or
- (6) carbocyclo;

R<sup>3</sup> and R<sup>4</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) aryl;
- (d) heterocyclo;
- (e) carbocyclo; or
- (f) when R<sup>3</sup> and R<sup>4</sup> are bonded to a common nitrogen atom, R<sup>3</sup> and R<sup>4</sup> may be joined, together with that nitrogen atom, to form a heterocyclic ring system;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) aryl;
- (d) carbocyclo;
- (e) fluorenyl;
- (f) heterocyclo;
- (g) R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> may, independently, be joined, together with the carbon atom to which they are bonded, to form a mono-, bi- or tricyclic carbocyclic ring system, or a mono-, bi- or tricyclic heterocyclic ring system;
- (h) alkynyl; or
- (i) alkenyl;

R<sup>8</sup> is:

- (a) hydrogen;
- (b) alkyl;
- (c) R<sup>8</sup> and R<sup>9</sup> may be joined, together with the atoms to which they are bonded, to form a heterocyclic ring system; or
- (d) R<sup>8</sup> and R<sup>11</sup> may be joined, together with the atoms to which they are bonded, to form a heterocyclic

ring system;

R<sup>9</sup> and R<sup>9'</sup> are independently:

- (a) hydrogen;
- (b) alkyl;
- (c) alkenyl;
- (d) alkynyl;
- (e) aryl;
- (f) heterocyclo;
- (g) carbocyclo;
- (h) R<sup>9</sup> may be joined together with R<sup>8</sup> as described above; or
- (i) R<sup>9</sup> and R<sup>9'</sup> may be joined, together with the carbon atom to which they are bonded, to form a carbocyclic group;

R<sup>10</sup> is:

- (a) hydrogen;
- (b) alkyl;
- (c) alkenyl;
- (d) alkynyl;
- (e) carbocyclo;
- (f) aryl; or
- (g) R<sup>10</sup> and R<sup>11</sup> taken together may form a bond to give a keto group;

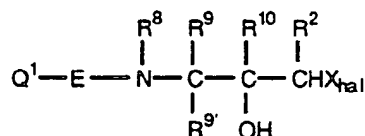
R<sup>11</sup> is:

- (a) hydrogen;
- (b) a hydroxyl protecting group;
- (c) R<sup>11</sup> may be joined together with R<sup>8</sup> as described above; or
- (d) R<sup>11</sup> may, together with R<sup>10</sup>, form a bond to give a keto group as described above;

Z is oxygen or sulfur; and

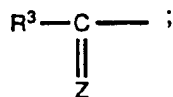
p and q are, independently, integers from 0 to 4;  
or a salt thereof.

26. A method for the preparation of a halohydrin of the following formula:



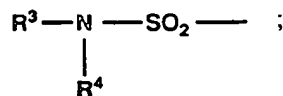
where Q<sup>1</sup> is

(1)



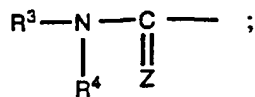
(2) R<sup>3</sup>-SO<sub>2</sub>-;

(3)



(4)

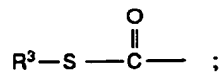
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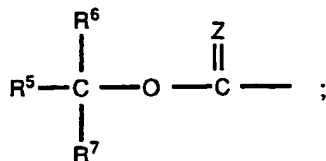
(5)

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(6)

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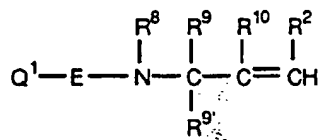
or

(7)  $\text{R}^3\text{-SO-}$ 

30

and E, Z,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{9'}$  and  $\text{R}^{10}$  are as defined in claim 1, and  $\text{X}_{\text{hal}}$  is chloro or bromo, comprising the step of contacting an olefin of the following formula:

35

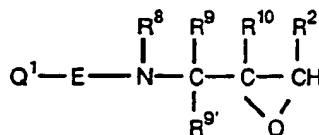


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with the compound  $\text{HOX}_{\text{hal}}$ .

27. The method of claim 26, wherein said method comprises the further step of contacting said halohydrin with a base to form an epoxide of the following formula:

45



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28. A compound of any one of claims 1-21 for use in treating conditions which require inhibition of HIV protease.

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